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Documents normally scheduled on a day that will be a Federal holiday will be published the next work day following the holiday.

Comments on this program are still invited. Comments should be submitted to the Day-of-the-Week Program Coordinator, National Archives and Records Service, General Services Administration, Washington, D.C. 20408.

ATTENTION: Questions, corrections, or requests for information regarding the contents of this issue only may be made by dialing 202-523-5286. For information on obtaining extra copies, please call 202-523-5240.
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reminders

(The items in this list were editorially compiled as an aid to Federal Register users. Inclusion or exclusion from this list has no legal significance. Since this list is intended as a reminder, it does not include effective dates that occur within 14 days of publication.)

**List of Public Laws**

This is a continuing numerical listing of public laws which have become law, together with the law number, the title, the date of approval, and the U.S. Statutes citation. The list is kept current in the Federal Register and copies of the laws may be obtained from the U.S. Government Printing Office.

S. 3435. Pub. Law 94-394
To increase an authorization of appropriations for the Privacy Protection Study Commission, and to remove the fiscal year expenditure limitation
(Sept. 3, 1976; 90 Stat. 1198)

H.R. 3052. Pub. Law 94-396
To amend section 512(b)(5) of the Internal Revenue Code of 1954 with respect to the tax treatment of the gain on the lapse of options to buy or sell securities
(Sept. 3, 1976; 90 Stat. 1201)

To provide assistance to the Government of Guam, to guarantee certain obligations of the Guam Power Authority, and for other purposes
(Sept. 3, 1976; 90 Stat. 1199)
Title 3—The President

PROCLAMATION 4454

United Nations Day, 1976

By the President of the United States of America

A Proclamation

On October 24 we will observe the 31st anniversary of the United Nations Charter, adopted in 1945 by governments determined to prevent a repetition of world war, to encourage the development of human rights and justice, and to remove the underlying causes of conflict by promoting economic and social progress for all nations.

The United States has played a leading role in encouraging the Organization to fulfill the promise of the Charter. We, and the rest of mankind, have benefited greatly from the vital contributions made by the Organization, particularly the Security Council, to the maintenance of world peace—the most striking reminder being the current peacekeeping role of the United Nations in the Middle East.

The United Nations has also been a forum for other areas of international concern: conferences to work out laws to govern the use of the oceans, to promote arms control, and to focus world attention on such problems as human rights, health, education, and hunger; new programs to promote trade and economic developments; and other activities designed to solve many of the new problems associated with independence in today’s world.

NOW, THEREFORE, I, GERALD R. FORD, President of the United States of America, do hereby designate Sunday, October 24, 1976, as United Nations Day. I urge the citizens of this Nation to observe that day with community programs that will promote the United Nations and its affiliated agencies.

I have appointed Edgar Speer to be United States National Chairman for United Nations Day and, through him, I call upon State and local officials to encourage citizens' groups and all agencies of communication to engage in appropriate observances of United Nations Day in cooperation with the United Nations Association of the United States of America and other interested organizations.

IN WITNESS WHEREOF, I have hereunto set my hand this seventh day of September in the year of our Lord nineteen hundred seventy-six, and of the Independence of the United States of America the two hundred and first.

[FR Doc.76-26493 Filed 9-7-76; 12:36 pm]
THE PRESIDENT

PROCLAMATION 4455

Columbus Day, 1976

By the President of the United States of America

A Proclamation

In this our Bicentennial year, we owe special tribute to the great Italian explorer whose historic voyage to the new world opened the way to the founding of these United States.

Sustained by the vision and financial support of Queen Isabella I of Spain, Christopher Columbus established the first permanent European settlement in the Americas, paving the way for the generations of immigrants from all over the world who came to build a new nation. This great achievement marked the beginning of a new era in the history of mankind.

As the heirs to the spirit and determination of Christopher Columbus, we are proud to honor his memory and unshakable courage and faith which made his epic journey a reality nearly five centuries ago.

In tribute to the achievement of Columbus, the Congress of the United States, by joint resolution approved April 30, 1934 (48 Stat. 657, 36 U.S.C. 146), as modified by the Act of June 28, 1968 (82 Stat. 250, 5 U.S.C. 6103(a) and note), requested the President to proclaim the second Monday in October of each year as Columbus Day.

NOW, THEREFORE, I, GERALD R. FORD, President of the United States of America, do hereby designate Monday, October 11, 1976, as Columbus Day; and I invite the people of this Nation to observe that day in schools, churches and other suitable places with appropriate ceremonies in honor of the great explorer.

I also direct that the flag of the United States be displayed on all public buildings on the appointed day in memory of Christopher Columbus.

IN WITNESS WHEREOF, I have hereunto set my hand this seventh day of September, in the year of our Lord nineteen hundred seventy-six, and of the Independence of the United States of America the two hundred and first.

[FR Doc.76-26573 Filed 9-7-76; 4:35 pm]

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
National Forest Products Week, 1976

By the President of the United States of America

A Proclamation

In the Nation's first century, Americans viewed their forests primarily as a source of survival and economic growth. In our second century, we continue to depend upon our forest resources for fuel, timber and sustenance, but we recognized the limits of our natural resource heritage and initiated action to conserve and manage our forests for future generations.

Fortunately, as we begin our third century, we have developed important tools to balance the needs of a growing population, our desire for an ever-improving standard of living, and concern for environmental quality.

Forestry research continues to make progress in achieving maximum efficient utilization of forest resources. In addition, strong Federal, State, and local forestry programs have been established to foster sound management of publicly owned forest lands and to encourage private forest landowners, through education, technical assistance, and grants, to practice sound forestry management on their lands. This cooperation among Federal, State, and private sectors is essential if we are to continue to provide the forest products our people require.

In order to emphasize America's reliance on forest resources and products, and to recognize their contribution in providing this Nation with consumer products, transportation systems, jobs and capital for economic growth, the Congress, by joint resolution of September 13, 1960 (74 Stat. 898; 36 U.S.C. 163), has designated the seven-day period beginning the third Sunday of October in each year as National Forest Products Week and has requested the President to issue annually a proclamation calling for its appropriate observance.

NOW, THEREFORE, I, GERALD R. FORD, President of the United States of America, do hereby call upon the people of the United States to observe the week beginning Sunday, October 17, 1976, as National Forest Products Week, with activities and ceremonies designed to invite public attention to the forest resources with which we are blessed and from which we have benefited, both materially and spiritually.

IN WITNESS WHEREOF, I have hereunto set my hand this eighth day of September, in the year of our Lord nineteen hundred seventy-six, and of the Independence of the United States of America the two hundred and first.

[FR Doc.76-26637 Filed 9-8-76; 11:33 am]
The President's Commission on Olympic Sports

By virtue of the authority vested in me as President of the United States, Section 4(c) of Executive Order No. 11868 of June 19, 1975, is hereby amended to read as follows:

"Sec. 4(c) The second report shall be an analysis of the organizational and developmental problems in each Olympic sport. This shall be submitted no later than January 15, 1977, and contain an analysis of the financial and facilities requirements of each sport and recommend ways to provide needed funds."

THE WHITE HOUSE,
September 8, 1976.

[FR Doc.76-26638 Filed 9-8-76;11:34 am]
rules and regulations

This section of the FEDERAL REGISTER contains regulatory documents having general applicability and legal effect most of which are key to and codified in the Code of Federal Regulations, which is published under 59 titles pursuant to 44 U.S.C. 1510.

The Code of Federal Regulations is sold by the Superintendent of Documents. Prices of new books are listed in the first FEDERAL REGISTER issue of each month.

Title 7—Agriculture

CHAPTER IX—AGRICULTURAL MARKETING SERVICE (MARKETING AGREEMENTS AND ORDERS; FRUITS, VEGETABLES, NUTS), DEPARTMENT OF AGRICULTURE

[Valencia Orange Reg. 544]

PART 908—VALENCIA ORANGES GROWN IN ARIZONA AND DESIGNATED PART OF CALIFORNIA

Limitation of Handling

PREAMBLE

This regulation fixes the quantity of California-Arizona Valencia oranges that may be shipped to fresh market during the weekly regulation period Sept. 10-16, 1976. It is issued pursuant to the Agricultural Marketing Agreement Act of 1937, as amended, and Marketing Order No. 908. The quantity of Valencia oranges so fixed was arrived at after consideration of the total available supply of Valencia oranges, including quantities of Valencia oranges currently available for market, the fresh market demand for Valencia oranges, Valencia orange prices, and the relationship of season average returns to the parity price for Valencia oranges.

§ 908.344 Valencia Orange Regulation 544.

(a) Findings. (1) Pursuant to the marketing agreement, as amended, and Order No. 908, as amended (7 CFR Part 908), regulating the handling of Valencia oranges grown in Arizona and designated part of California, effective under the applicable provisions of the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601-674), and upon the basis of the recommendation and information submitted by the Valencia Orange Administrative Committee, established under the said amended marketing agreement and order, and upon other available information, it is hereby found that the limitation of handling of such Valencia oranges, as hereinafter provided, will tend to effectuate the declared policy of the act.

(2) The need for this regulation to limit the respective quantities of Valencia oranges that may be marketed from District 1, District 2, and District 3 during the ensuing week stems from the production and marketing situation confronting the Valencia orange industry.

(i) The Administrative Committee has submitted its recommendation with respect to the quantities Valencia oranges that should be marketed during the next succeeding week. Such recommendation, designed to provide adequate marketing opportunity to handlers in all districts, resulted from consideration of the factors enumerated in the order. The committee further recommends that the fresh market demand for Valencia oranges is stronger. Prices for b.o.b. cartons during the week ending September 2 were $3.54 per carton on 582 cars as compared with $3.53 per carton on 583 cars during the prior week. Truck and rolling supplies at 541 cars were up 76 cars from last week.

(II) Having considered the recommendation and information submitted by the committee, and other available information, the Secretary finds that the respective quantities of Valencia oranges which may be marketed during the next succeeding week stems from the handling of lemons grown in Arizona and designated part of California, pursuant to said marketing agreement, as amended, and Marketing Order No. 908--VALENCIA ORANGES.

(1) Pursuant to said marketing agreement, as amended, and Marketing Order No. 908, the handling of Valencia oranges may be handled in accordance with the provisions of this regulation until 30 days after publication hereof in the FEDERAL REGISTER (5 U.S.C. 553) because the time intervening between the date when information upon which this regulation is based became available and the time when this regulation must become effective in order to effectuate the declared policy of the act is insufficient, and a reasonable time is permitted, under the circumstances, for preparation for such effective time; and good cause exists for making the provisions hereof effective as hereinafter set forth. The committee held an open meeting during the current week; after giving due notice thereof, to consider supply and market conditions for Valencia oranges and the need for regulation; interested persons were accorded an opportunity to submit information and views at this meeting; the recommendation and supporting information for regulation during the period specified herein were promptly submitted to the Department after such meeting was held; the provisions of this regulation, including its effective time, are identical with the aforementioned recommendation of the committee, and information concerning such provisions and effective time has been disseminated among handlers of such Valencia oranges. The committee meeting was held on September 7, 1976.

(b) Order. (1) The respective quantities of Valencia oranges grown in Arizona and designated part of California for the period specified herein will not require any special preparation on the part of persons subject hereto which cannot be completed on or before the effective date hereof. Such committee meeting was held on September 7, 1976.

(ii) Having considered the recommendation and information submitted by the committee, and other available information, it is hereby further found that it is impracticable and contrary to the public interest to give preliminary notice, engage in public rule-making procedure, and postpone the effective date of this regulation until 30 days after publication hereof in the FEDERAL REGISTER (5 U.S.C. 553) because the time intervening between the date when information upon which this regulation is based became available and the time when this regulation must become effective in order to effectuate the declared policy of the act is insufficient, and a reasonable time is permitted, under the circumstances, for preparation for such effective time; and good cause exists for making the provisions hereof effective as hereinafter set forth. The committee held an open meeting during the current week; after giving due notice thereof, to consider supply and market conditions for Valencia oranges and the need for regulation; interested persons were accorded an opportunity to submit information and views at this meeting; the recommendation and supporting information for regulation during the period specified herein were promptly submitted to the Department after such meeting was held; the provisions of this regulation, including its effective time, are identical with the aforementioned recommendation of the committee, and information concerning such provisions and effective time has been disseminated among handlers of such Valencia oranges. The committee meeting was held on September 7, 1976.

(ii) Having considered the recommendation and information submitted by the committee, and other available information, it is hereby further found that it is impracticable and contrary to the public interest to give preliminary notice, engage in public rule-making procedure, and postpone the effective date of this regulation until 30 days after publication hereof in the FEDERAL REGISTER (5 U.S.C. 553) because the time intervening between the date when information upon which this regulation is based became available and the time when this regulation must become effective in order to effectuate the declared policy of the act is insufficient, and a reasonable time is permitted, under the circumstances, for preparation for such effective time; and good cause exists for making the provisions hereof effective as hereinafter set forth. The committee held an open meeting during the current week; after giving due notice thereof, to consider supply and market conditions for Valencia oranges and the need for regulation; interested persons were accorded an opportunity to submit information and views at this meeting; the recommendation and supporting information for regulation during the period specified herein were promptly submitted to the Department after such meeting was held; the provisions of this regulation, including its effective time, are identical with the aforementioned recommendation of the committee, and information concerning such provisions and effective time has been disseminated among handlers of such Valencia oranges. The committee meeting was held on September 7, 1976.

Dated: September 8, 1976.

CHARLES E. BEEZER,
Deputy Director, Fruit and Vegetable Division, Agricultural Marketing Service.

[FR Docket 75-9554; Filed 9-8-76; 8:45 a.m.]

PART 910—LEMONS GROWN IN THE STATES OF CALIFORNIA AND ARIZONA

Expenses and Rate of Assessment

This document authorizes expenses of $378,000 for the Lemon Administrative Committee, under Marketing Order No. 910, for the 1976-77 fiscal year and fixes a rate of assessment of $0.5315 per carton of lemons handled in such period to be paid to the committee by each handler as his pro rata share of such expenses.

On August 11, 1976, notice of proposed rulemaking was published in the Federal Register (41 FR 23,922) regarding proposed expenses and the proposed rate of assessment, pursuant to the marketing agreement, as amended, and Order No. 910, as amended (7 CFR Part 910), regulating the handling of lemons grown in the States of California and Arizona. This notice allowed interested persons to submit data, views, or arguments pertaining to these proposals. None were submitted. This regulatory program is effective under the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601-674). After consideration of all relevant matters presented, including the proposals set forth in such notice, which were submitted by the Lemon Administrative Committee (established pursuant to said marketing agreement and order), it is hereby found and determined that:

§ 910.214 Expenses and rate of assessment.

(a) Expenses. Expenses that are reasonable and likely to be incurred by the Lemon Administrative Committee during the period August 1, 1976, through July 31, 1977, will amount to $378,000.

(b) Rate of assessment. The rate of assessment for said period payable by each handler in accordance with § 910.214, is fixed at $0.5315 per assessable carton of lemons.

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
It is hereby further found that good cause exists for not postponing the effective date hereof until 30 days after publication in the Federal Register (36 U.S.C. 553) in that (1) shipments of the current crop of lemons grown in the designated production area are now being made; (2) the relevant provisions of said marketing agreement and this part require that the rate of assessment herein fixed shall be applicable to all assessable lemons handled during the aforesaid period, and such period begins on August 1, 1976, and said rate of assessment will automatically apply to all such lemons beginning with such date.

(Docs. 1-19, 48 Stat. 31, as amended; 7 U.S.C. 651-676)

DATED: September 2, 1976.

CHARLES R. BRADER, Deputy Director, Fruit and Vegetable Division, Agricultural Marketing Service.

[FR Doc.76-26312 Filed 9-4-76; 8:45 am]

CHAPTER XIV—COMMODITY CREDIT CORPORATION, DEPARTMENT OF AGRICULTURE

SUBCHAPTER B—LOANS, PURCHASES, AND OTHER OPERATIONS


PART 1421—GRAINS AND SIMILARLY HANDLED COMMODITIES

Subpart—1976 Crop Rice Loan and Purchase Program

Rice: Changes in Rates

The regulations issued by the Commodity Credit Corporation (CCC) and published on June 14, 1976, at 41 FR 23930, which set forth specific requirements with respect to loans and purchases for the 1976 crop of rice, are hereby amended to increase the loan rates for rice. This increase reflects the change in the index of prices paid by farmers for production items, interest, taxes, and wage rates during the period beginning on the date of enactment and ending July 31, 1976, as required by the Rice Production Act of 1975 (Pub. L. 94-214, 90 Stat. 181, approved February 16, 1976). It is impracticable and contrary to the public interest to give effect to the proposed rulemaking with respect to this amendment because 1976 crop rice is currently being harvested and it is essential that the rates provided for in this subpart be put into effect with respect to such rice on the earliest possible date.

Paragraphs (a) and (c) of § 1421.328 are hereby revised to increase the loan rates for farm-storage and warehouse-storage rice. Accordingly, 7 CFR, 1421.328 (a) and (c) are revised to read as follows:

§ 1421.328 Loan and purchase rates.

(a) Farm storage loans. The loan rate for farm-storage rice shall be $6.19 per hundredweight for any class. The settlement rate shall be the applicable basic rate specified in paragraph (c) of this section, adjusted in accordance with the

provision of this section and §§ 1421.310 and 1421.32.

(c) Basic rates. The basic rate per 100 pounds of rice shall be computed as follows: Multiply the milling yield (in pounds per hundredweight) of whole kernels by the applicable loan rate for whole kernels (as shown in the table below according to class) and round the result to the nearest hundredth. Similarly multiply the difference between the total milling yield and the whole kernels milling yield (in pounds per hundredweight) by the applicable loan rate for broken rice and round the result to the nearest hundredth. Add the results (as rounded) of these two computations to obtain the basic loan or purchase rate per 100 pounds of rice and express such rate in dollars and cents.

Loan rates for whole kernels and broken rice

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<th>Rough rice class</th>
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<th>Broken rice</th>
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<td>Short</td>
<td>9.25 4.75</td>
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Effective date: This amendment takes effect on September 5, 1976.

Signed at Washington, D.C., on September 2, 1976.

KENNETH E. FRIED, Executive Vice President, Commodity Credit Corporation.

[FR Doc 76-26370 Filed 9-4-76; 8:45 am]

CHAPTER XVIII—FARMERS HOME ADMINISTRATION, DEPARTMENT OF AGRICULTURE

SUBCHAPTER A—GENERAL REGULATIONS

[FmHA Instruction 410.1]

PART 1801—RECEIVING AND PROCESSING APPLICATIONS

Subpart A—Receiving and Processing Applications

Section 1801.1 of Subpart A, Part 1801 of Chapter XVIII, Title 7, Code of Federal Regulations (36 FR 18727, Redesignated at 38 FR 4772; 41 FR 14860; 41 FR 28676) is amended. This amendment is required to comply with the revised Real Estate Settlement Procedures Act and the Department of Housing and Urban Development’s Regulations.

This amendment is not published for proposed rulemaking, but includes its effect to provide for FmHA compliance with the Real Estate Settlement Procedures Act and regulations issued by the Department of Housing and Urban Development.

Sections 1801.2(1) and 1801.2(2) (1) and (2) are amended to make references to the information booklet entitled “Settlement Costs,” and to Form FmHA 440-58, “Estimate of Settlement Costs” which replaces Exhibit A to Subpart I of Part 1801 if this chapter, entitled, “Assignment to Special Information Booklet”.

As amended, § 1801.2 reads as follows:

§ 1801.2 Receiving applications.

(1) For all loans and credit sales secured by a first mortgage and involving the purchase of an existing 1 to 4 family home or purchase of a building site and construction of 1 to 4 family residential units, the booklet entitled “Settlement Costs” will be hand-delivered to the applicant when the completed application is received or mailed to the applicant within three (3) business days after receipt of the application in the County Office.

(2) A record of the date and method of delivery of the booklet and Form FmHA 440–58 will be kept in the running record section of the applicant/borrower County Office case folder.

Dated: August 27, 1976.

JOSEPH R. HANSON, Acting Administrator, Farmers Home Administration.

[FR Doc 76-26371 Filed 9-4-76; 8:45 am]

SUBCHAPTER E—LOANS AND GRANTS PRIMARILY FOR REAL ESTATE PURPOSES

[FmHA Instruction 443.1]

PART 1821—FARM PURCHASE AND DEVELOPMENT LOANS TO INDIVIDUALS

Subpart A—Farm Ownership Loan Policies, Procedures, and Authorizations

Sections 1821.4(a), 1821.7(b), and 1821.11(a) of Subpart A of Part 1821, Title 7, Code of Federal Regulations (30 FR 72655) are revised. Section 1821.4(a) is revised to include in the definition of a farm a residence physically separate from the farm acreage if it is ordinarily treated as part of the farm in the community. The revision to § 1821.7(b) removes the material in the “note” following paragraph (f) and incorporates its contents into § 1821.11 (a). As revised, § 1821.11(a) will allow use of buildings owned by the applicant and not located on the farm; specify the requirements of farm dwellings financed with rural housing funds; and allow use of a mobile home as a dwelling when the mobile home is already owned by the applicant. Relieving certain restrictions, these revisions make the farm ownership program available to more present and future farmers. The revision is designed to meet the current
needs of these farmers, as evidenced by the many applications already received for loans, amended regulations contained herein. Delay in the processing of these applications caused by a delay in the effective date of this revision is contrary to the public interest. Notice and public procedure are therefore unnecessary. However, it is the policy of this Department that rules relating to public property, loans, grants, and opportunities shall be published for comment notwithstanding the exemption in 5 U.S.C. 553 with respect to such rules. In accordance with the spirit of that policy, interested persons may submit written comments, suggestions or arguments to the Office of the Chief, Directives Management Branch, Farmers Home Administration, United States Department of Agriculture, Room 6316, South Building, Washington, DC 20250, on or before October 12, 1976. Material thus submitted will be evaluated and acted upon in the same manner as if this document were a proposal. All written submissions made pursuant to this notice will be made available for public inspection at the Office of the Chief, Directives Management Branch, during regular business hours (8:15 a.m.-4:45 p.m.). Section 1821.4(a) and 1821.11(a) of Part 1821 as revised, however, will remain effective until they are, further revised or amended. As revised, §1821.4(a) reads as follows:

§1821.4 Definitions.

(a) Farm. The term "farm" includes a tract or tracts of land, improvements, and other appurtenances considered to be farm property, and owned or to be acquired by the applicant, used or to be used in the production of crops or livestock including the production of fish under controlled conditions. The term "farm" also includes any such land and improvements and facilities used in a nonfarm enterprise. It will also include a residence which, although physically separate from farm acreage, is ordinarily treated as part of the farm in the local community.

Section 1821.11(a) is revised to read as follows:

§1821.11 Special Requirements.

(a) Dwellings and other essential buildings. (1) Buildings adequate for the planned operation of the farm, including any nonfarm enterprise, must be available for the applicant's use after the loan is made. The necessary buildings ordinarily will be located on the applicant's farm if an applicant who already owns an adequate, decent, safe, and sanitary dwelling suitable for the family's needs, which is located close enough to the farm to be operated successfully, it will not be necessary to provide a dwelling on the farm. A real estate lien will be taken on such dwelling. In an unusual case, an exception to the requirement that the buildings include a suitable dwelling may be made when the applicant has a long-term lease on acceptable rented buildings that are adjacent to or near the farm, or the applicant occupies suitable buildings of relatives that he will eventually inherit or be permitted to purchase.

(2) When provision of a dwelling is required, if the applicant is eligible for an RH loan, an RH loan will be processed simultaneously with the FO docket. Dwellings will meet the requirements for RH loans required in Subpart A of Part 1822 of this chapter.

(3) If the farm does not have an adequate dwelling and the applicant owns a mobile home which he uses or plans to use as his residence, the applicant will not be required to build a dwelling.

(7 U.S.C. 1989, 42 U.S.C. 1450; delegation of authority by the Secretary of Agriculture, 7 CFR 223, delegation of authority by the Assistant Secretary for Rural Development, 7 CFR 2.70.)

Effective date: This amendment is effective September 9, 1976.

Dated: September 1, 1976.

JOSEPH R. HANSON, Acting Administrator, Farmers Home Administration.

[FR Doc. 76-26372 Filed 9-8-76; 8:45 am]

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PART 1901—PROGRAM-RELATED INSTRUCTIONS

Subpart J—Grant-In-Aid Information

INTER-GOVERNMENTAL COOPERATION ACT—SECTION 201—TREASURY CIRCULAR—1082

There is hereby established under chapter XXVIII, Title 7, Code of Federal Regulations (41 FR 18158; 41 FR 26577) an amendment which replaces Exhibit A, "Attachment to Special Information Booklet," to "Settlement Costs" booklet and provides for a form to replace Exhibit A of this subpart. This amendment is necessary to comply with the revised Real Estate Settlement Procedures Act and the Department of Housing and Urban Development's Regulation.

Specifically, this amendment makes the following changes:

1. Section 1901.406(c) (1) is amended to make reference to the information booklet entitled "Settlement Costs." This amendment changes a reference made from the "Special Information Booklet" to "Settlement Costs" booklet and provides for a form to replace Exhibit A of this subpart. This form replaces Exhibit A, "Attachment to Special Information Booklet" which is deleted.

2. Section 1901.406(c) (1) (i) and (ii) are amended to make reference to Form FHMA 440-58, "Estimate of Settlement Costs" which is given to applicants. This form replaces Exhibit A, "Attachment to Special Information Booklet" which is deleted.

This amendment is not published for Proposed Rulemaking because its effect is to provide for FHMA compliance with the Real Estate Settlement Procedures Act and regulations issued by the Department of Housing and Urban Development.

§1901.406 Real estate settlement procedures.

(c) Actions required. (1) The information booklet entitled, "Settlement Costs," will either be given to the applicant at the time the completed application is received or mailed to the applicant no later than three (3) business days after receipt of the application in the County Office.

(1) Form FHMA 440-58 "Estimate of Settlement Costs" is to be used to provide a "good faith" statement of estimated closing costs. Form FHMA 440-58 will be completed by the County Supervisor and mailed or delivered to the applicant with the Settlement Costs booklet.

(2) Form FHMA 440-58 does not replace Truth-In-Lending forms. Appropriate forms listed in §1901.401 will continue to be required.

Effective date: This amendment is effective September 9, 1976.

Dated: August 27, 1976.

JOSEPH R. HANSON, Acting Administrator, Farmers Home Administration.
authority by the Asst. Sec. for Rural Development, 7 CFR 2.70; delegations of authority by Dir. OEO 20 FR 14769, 39 FR 8699.

§ 1901.451 Purpose.

This subpart outlines the procedures that the Farmers Home Administration (FmHA) must follow to comply with section 201 of the Intergovernmental Cooperation Act of 1968 as set forth in the Department of Treasury Circular Number 150. (This section required that Federal agencies administering grant-in-aid programs to State Governments or their political subdivisions must notify the Governor and the legislature of any State, on the request of either the Governor or the legislature, information on the amounts and purposes of all grants under the program in that State.)

§ 1901.452 Policy.

FmHA will provide the required information to the State Central Information Reception Agency (SCIRA) (an agency designated by the Governor of a State, in consultation with the legislature, to serve as the central reception point in a State for Federal grant-in-aid information) about the following grants approved on or after July 1, 1970: (a) Grants for self-help technical assistance under Pub. L. 90-448. (b) Grants for facilitating the development of private business enterprises under Pub. L. 92-419 (Industrial Development Grants). (c) Grants for development of water and waste disposal facilities under Pub. L. 92-444. (d) Grants to provide low rent housing for domestic farm labor under Pub. L. 92-559.

§ 1901.453 Authorities and responsibilities.

The State Director, for the grants listed in § 1901.452, will: (a) Notify SCIRA using section III of Standard Form 424, "Federal Assistance," within 7 days after approval of an initial or subsequent grant or after a change in the amount or purpose of a grant. One copy of the notification will be sent to SCIRA and clearinghouse. However, additional copies may be supplied on request.

(b) Keep current the name and address of the SCIRA. See Exhibit A, "Directory of State Clearinghouses and State Central Information Reception Agencies (for A-95/TC-1083 use)."

§ 1901.454 [Reserved]

§ 1901.455 Preparation of Standard Form 424.

This form will be obtained from the Finance Office, St. Louis, Missouri. See Exhibit B for guidance in completing Standard Form 424 for grants listed in § 1901.452. The date of the application (on Form AD-823, "Application for Federal Assistance (Construction Projects)" for Water and Waste Disposal and Industrial Development grants, and on Form AD-825, "Application for Federal Assistance (Short Form)" for Technical Assistance grants) will be used as the "application received" date in Item 25 of Standard Form 424. In addition to copies of SCIRA and clearinghouse, a copy will be sent to the National Office (and to the US Department of Agriculture, Office of Management and Finance, 14th and Independence Avenue, SW., Washington, D.C. 20250.)

§ 1901.456 Function of the SCIRA.

In each State, this Agency will: (a) Distribute information about FmHA grants available to the State and its political subdivisions provided by the State Director to the Governor, the State legislature, and other agencies of the State that the Governor may designate.

(b) Make the information available to regional and metropolitan agencies and to local governments of the State.

§§ 1901.457–1901.500 [Reserved]

EXHIBIT A—DIRECTORY OF STATE CLEARINGHOUSES AND STATE CENTRAL INFORMATION RECEPTION AGENCIES (FOR A-95/TC-1083 USE)

The following addresses should be sent Federal assistance action notices in compliance with Circular A-95 for Clearinghouse, and in compliance with Circular TC-1083 for State Central Information Reception.

Agencies (SCIRAS). Note that in 44 States the address of the State Clearinghouse and the SCIRA is the same. A single notification will suffice when both A-95 and TC-1083 compliance (at State level) is required. Appropriate areawide clearinghouse addresses must also be informed as applicable under A-95. Please note, the State Clearinghouse and the SCIRA are different addresses in the States of Vermont, New Jersey, Illinois, Colorado, Nevada, and Hawaii. The list will be updated periodically, at least on an annual basis.

Alabama:

Alabama Development Office, State Office Building, Montgomery, Alabama 36104.

Alaska:


Arizona:

Dept. of Economic Planning and Development, Arizona State Clearinghouse, 1024 West Main Street, Phoenix, Arizona 85007.

Arkansas:

Department of Planning, 400 Train Station Square, Little Rock, Arkansas 72201, Fred Kleinhauer (501) 687-2311.

California:

Office of the Governor, Office of Planning and Research, 1400 Tenth Street, Sacramento, California 95814.

Colorado (2):

(1) State Clearinghouse: Division of Planning, Department of Local Affairs, 1845 Sherman Street, Denver, Colorado 80203.

(2) SCIRA: Office of State Planning & Budgeting, 172 State Services Building, Denver, Colorado 80203, Gary Reals (303) 445-0613.

Connecticut:

Office of Intergovernmental Programs, 340 Capitol Avenue, Hartford, Connecticut 06115.

Delaware:

State Planning Office, Thomas Collins Building, 639 S. Dupont Highway, Dover, Delaware 19901.

Florida:

Bureau of Intergovernmental Relations, Division of State Planning, 401 Apalachee Parkway, Tallahassee, Florida 32304.

Georgia:

Office of Planning and Budget, Attention: Clearinghouse, 270 Washington Street, SW., Atlanta, Georgia 30334.

Hawaii (2):

(1) State Clearinghouse: Department of Planning and Economic Development, P.O. Box 2359, Honolulu, Hawaii 96820.

(2) SCIRA: State of Hawaii, Department of Budget and Finance, P.O. Box 150, Honolulu, Hawaii 96819.

Idaho:

Division of Budget, Policy Planning and Coordination, State House, Boise, Idaho 83720.

Illinois (2):


(2) State of Illinois, Commission on Intergovernmental Cooperation, 217 S. First Street, Springfield Illinois 62703.

Indiana:

Indiana State Budget Agency, 312 State House, Indianapolis, Indiana 46204.

Iowa:

Office of Planning and Programming, 533 East 12th Street, Des Moines, Iowa 50310.

Kansas:

Division of Planning and Research, Department of Administration, State Office Building, Topeka, Kansas 66601.

Kentucky:

State Clearinghouse, Office for Local Government, Capitol Annex, Room 337, Frankfort, Kentucky 40601.

Louisiana:

Office of Intergovernmental Relations, P.O. Box 44455, Baton Rouge, Louisiana 70808.

Maine:

Executive Department, Maine State Clearinghouse, 184 State Street, Augusta, Maine 04333, Allen G. Peace (207) 289-3201.

Maryland:

Department of State Planning, 201 W. Preston Street, Baltimore, Maryland 21202.

Massachusetts:

Office of State Planning, John McCormack Building, 1 Ashburton Place, Boston, Massachusetts 02108.

Michigan:

Department of Management and Budget, Office of Intergovernmental Relations, Federal Aid Management Division, Lewis Cass Building, Lansing, Michigan 48913.

Minnesota:


Mississippi:

Coordinator Federal-State Programs, Office of the Governor, 400 Watkins Building, 510 George Street, Jackson, Mississippi 39201.

Missouri:

Office of Administration, State Planning and Analysis Div., P.O. Box 800, State Capitol Building, Jefferson City, Missouri 65101, Terry Rohms (314) 765-4834.

Montana:

Research and Information Systems Division, Department of Community Affairs, 1424 9th Avenue, Helena, Montana 59601.

Nebraska:

Office of Planning and Programming, Box 94601, State Capitol, Lincoln, Nebraska 68509.
Vermont:
- State Planning Office, Pavilion Office Building, Montpelier, Vermont 05602.
- SCIRA: Department of Budget and Management, Pavilion Office Building, Montpelier, Vermont 05602.

Virginia:
- Division of State Planning and Community Affairs, 1010 Madison Building, Richmond, Virginia 23219, Charles A. Christophersen.
- Grant Information Department, Office of Federal-State Relations, State Capitol Building, Charleston, West Virginia 25305.
- State Clearinghouse/Central Information Reception Agency, Department of Administration, Room 2-129, State Office Building, 1 West Wilton Street, Madison, Wisconsin 53702.

Wyoming:
- State Planning Coordinator, Office of the Governor, Capitol Building, Cheyenne, Wyoming 82002.
- District of Columbia:
  - Office of Budget and Management Systems, District Building, 14th and E Street, NW, Washington, D.C. 20004.
- Puerto Rico:
  - Planning Board, P.O. Box 9447, San Juan, Puerto Rico 00930.
- Virgin Islands:
  - Office of the Governor, P.O. Box 893, St. Thomas, Virgin Islands 00801.
- Guam:
  - Governor of Guam, Agana, Guam 96910.
- Samoa:
  - Planning and Budget Office, Government of American Samoa, Pago Pago, American Samoa 96799.

**FEDERAL ASSISTANCE**

<table>
<thead>
<tr>
<th>STATE</th>
<th>AGENCY</th>
<th>ADDRESS</th>
<th>ZIP 5 DIGITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WY</td>
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</tr>
</tbody>
</table>

**RULES AND REGULATIONS**

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
## GENERAL INSTRUCTIONS

Applicant will complete all items in Section 1. If an item is not applicable, write "N/A." If additional space is needed, insert an asterisk (*) and use the remarks section on the back of the form. An explanation follows for each item:

<table>
<thead>
<tr>
<th>Item</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mark appropriate box. Pre-application and application guidance is in FMG 24-7 and Federal agency program instructions. Notification of intent guidance is in Circular A-95 and procedures from clearinghouses. Applicant will not use the &quot;Report of Federal Action&quot; box.</td>
</tr>
<tr>
<td>2.</td>
<td>Applicant's own control number, if desired.</td>
</tr>
<tr>
<td>3.</td>
<td>Date Section I is prepared.</td>
</tr>
<tr>
<td>5.</td>
<td>Number assigned by State clearinghouse, or if delegated by State to statewide clearinghouse. All requests to Federal agencies must contain this identifier if the program is covered by Circular A-95 and required by applicable State/area-wide clearinghouse procedure. If in doubt, consult your clearinghouse.</td>
</tr>
<tr>
<td>7.</td>
<td>Use Catalog of Federal Domestic Assistance number assigned to program under which assistance is requested, if more than one program (e.g., joint-funding), write &quot;multiple&quot; and explain in remarks. If unknown, cite Public Law or U.S. Code.</td>
</tr>
<tr>
<td>11.</td>
<td>Brief title and appropriate description of project.</td>
</tr>
<tr>
<td>13.</td>
<td>Check the type(s) of assistance requested. The definitions of the terms are:</td>
</tr>
<tr>
<td>14.</td>
<td>A. Basic Grant. An original request for Federal funds. This would not include any contribution provided under a supplemental grant.</td>
</tr>
<tr>
<td>15.</td>
<td>B. Supplemental Grant. A request to increase a basic grant in certain cases where the eligible applicant cannot supply the required matching share of the basic Federal program (e.g., grants awarded by the Appalachian Regional Commission to provide the applicant a matching share).</td>
</tr>
<tr>
<td>18.</td>
<td>E. Other. Explain on remarks page.</td>
</tr>
<tr>
<td>19.</td>
<td>Governmental unit where significant and measurable impact could be observed. List only largest unit or units affected, such as State, county, or city. If entire unit affected, list it rather than subunits.</td>
</tr>
<tr>
<td>20.</td>
<td>Estimated number of persons directly benefiting from project.</td>
</tr>
<tr>
<td>21.</td>
<td>Use appropriate code letter. Definitions are:</td>
</tr>
<tr>
<td>22.</td>
<td>A. New. A substantive for the first time for a new project.</td>
</tr>
<tr>
<td>23.</td>
<td>B. Renewal. An extension for an additional funding/budget period for a project having no projected completion date, but for which Federal support must be renewed each year.</td>
</tr>
<tr>
<td>24.</td>
<td>C. Revision. A modification to project nature or scope which may result in funding change (increase or decrease).</td>
</tr>
<tr>
<td>25.</td>
<td>D. Continuation. An extension for an additional funding/budget period for a project the agency initially agreed to fund for a definite number of years.</td>
</tr>
<tr>
<td>26.</td>
<td>E. Augmentation. A requirement for additional funds for a project previously awarded funds in the same funding/budget period; Project nature and scope unchanged.</td>
</tr>
<tr>
<td>27.</td>
<td>F. Incurred. Do not identify if an item is not applicable.</td>
</tr>
<tr>
<td>31.</td>
<td>J. Cost at time of submission (costs shown in remarks).</td>
</tr>
<tr>
<td>32.</td>
<td>K. Total. Total amount requested or to be contributed during the period of the request.</td>
</tr>
<tr>
<td>33.</td>
<td>L. Decrease. Decrease in the amount funded.</td>
</tr>
<tr>
<td>34.</td>
<td>M. Increase. Increase in the amount funded.</td>
</tr>
<tr>
<td>35.</td>
<td>N. Equal. Amount requested or to be contributed equal to amounts already contributed.</td>
</tr>
<tr>
<td>36.</td>
<td>O. Increase. Increase in the amount contributed.</td>
</tr>
<tr>
<td>37.</td>
<td>P. Decrease. Decrease in the amount contributed.</td>
</tr>
<tr>
<td>38.</td>
<td>Q. Other. Explain on remarks page.</td>
</tr>
<tr>
<td>39.</td>
<td>R. Remaining. Remaining amount of a previous award.</td>
</tr>
<tr>
<td>40.</td>
<td>S. New. Self explanatory.</td>
</tr>
<tr>
<td>41.</td>
<td>T. Renumber. Self explanatory.</td>
</tr>
<tr>
<td>42.</td>
<td>U. Other. Explain on remarks page.</td>
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<tr>
<td>43.</td>
<td>V. Additional. Additional funds contributed to the project.</td>
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<tr>
<td>44.</td>
<td>W. Project. Project nature and scope of project.</td>
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<tr>
<td>45.</td>
<td>X. Additional. Additional funds contributed to the project.</td>
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<td>46.</td>
<td>Y. Project. Project nature and scope of project.</td>
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<tr>
<td>47.</td>
<td>Z. Additional. Additional funds contributed to the project.</td>
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<td>48.</td>
<td>AA. Project. Project nature and scope of project.</td>
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<td>49.</td>
<td>BB. Project. Project nature and scope of project.</td>
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<td>CC. Project. Project nature and scope of project.</td>
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<td>51.</td>
<td>DD. Project. Project nature and scope of project.</td>
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<td>52.</td>
<td>EE. Project. Project nature and scope of project.</td>
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<td>GG. Project. Project nature and scope of project.</td>
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<td>55.</td>
<td>HH. Project. Project nature and scope of project.</td>
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<td>56.</td>
<td>II. Project. Project nature and scope of project.</td>
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<td>57.</td>
<td>JJ. Project. Project nature and scope of project.</td>
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<td>58.</td>
<td>KK. Project. Project nature and scope of project.</td>
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<td>59.</td>
<td>LL. Project. Project nature and scope of project.</td>
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<td>MM. Project. Project nature and scope of project.</td>
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<td>NN. Project. Project nature and scope of project.</td>
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<td>63.</td>
<td>PP. Project. Project nature and scope of project.</td>
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<td>64.</td>
<td>QQ. Project. Project nature and scope of project.</td>
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<td>65.</td>
<td>RR. Project. Project nature and scope of project.</td>
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<td>66.</td>
<td>SS. Project. Project nature and scope of project.</td>
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<td>67.</td>
<td>TT. Project. Project nature and scope of project.</td>
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<td>68.</td>
<td>UU. Project. Project nature and scope of project.</td>
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<td>69.</td>
<td>VV. Project. Project nature and scope of project.</td>
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<td>70.</td>
<td>WW. Project. Project nature and scope of project.</td>
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<td>71.</td>
<td>WW. Project. Project nature and scope of project.</td>
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<tr>
<td>72.</td>
<td>XX. Project. Project nature and scope of project.</td>
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<tr>
<td>73.</td>
<td>YY. Project. Project nature and scope of project.</td>
</tr>
<tr>
<td>74.</td>
<td>ZZ. Project. Project nature and scope of project.</td>
</tr>
</tbody>
</table>

### STANDARD FORM 424 PAGE 3 (10-75)
RULINGS AND REGULATIONS

16. Appropriate data project expected to begin (usually associated with estimated dates of availability of funds).

17. Estimated number of months to complete project after Federal funds are available.

18. Estimated date of application/verification will be submitted to Federal agency if this project requires clearinghouse review. If review not required, this date would usually be some time in item 22c.

APPLICANT PROCEDURES FOR SECTION II

Applicants will always complete Items 23a, 23b, and 23c. If clearinghouse review is required, Item 23b must be fully completed. An explanation follows for each item.

23a. List clearinghouse to which submitted and show in appropriate block the status of their responses. If more than three clearinghouses, continue in remarks section. All written comments submitted by or through clearinghouses must be attached.

23b. Name and title of authorized representative of local applicant.

23c. Self explanatory.

Note: Applicant completes only Sections I and III. Section II is completed by Federal agencies.

FEDERAL AGENCY PROCEDURES FOR SECTION III

If applicant-supplied information is in Sections I and III, an updating or adjustment to fit the final Federal action, the Federal agency will complete Section III only. An explanation for each item follows.

24. Executive department or independent agency having administration responsibility.

25. Self explanatory.

26. Primary organizational unit below department level having direct program management responsibility.

27. Office directly monitoring the program.

28. Use to identify nonaward actions where Federal grant identifier in Item 30 is not applicable or will not suffice.

29. Complete address of administering office shown in Item 30.

30. Use to identify award actions where different from Federal application identifier in Item 28.

31. Self explanatory. Use remarks section to amplify where appropriate.

32. Amount to be contributed during the first funding/budget period by each contributor. Value of lending contributions will be included. If the action is a change in dollar amount of an existing grant (a revision), indicate only the amount of change. For decreases, enclose the amount in parentheses. If both basic and supplemental amounts are included, break out remarks. For multiple program funding, use totals and show program breakdown in remarks. Item definitions: 32a, amount awarded by Federal Government; 32b, amount applicant will contribute 32c, amount from State, if applicant is not a State; 32d, amount from local government if applicant is not a local government; 32e, amount from any other sources, explain in remarks.

33. Date action was taken on this request.

34. Date funds will become available.

Title 13—Business Credit and Assistance
CHAPTER I—SMALL BUSINESS ADMINISTRATION
[38161]
PART 107—SMALL BUSINESS INVESTMENT COMPANIES

Deposit of Idle Funds in Savings Account

On June 29, 1976, a notice of proposed rulemaking regarding an amendment to §107.808 of the SBA Regulations was published in the Federal Register (41 FR 26716) to expand current policy to permit licensees to deposit funds not needed for current operations in savings accounts in any bank which is insured by the Federal Deposit Insurance Corporation, within the limits set by Regulation "Q" issued by the Board of Governors of the Federal Reserve System.

Interested parties were given 30 days to submit comments and no adverse comment was received. Accordingly, the substance of the amendment then proposed and hereinafter set forth shall become effective September 9, 1976.

Section 107.808 is amended to read as follows:

§ 107.808 Idle funds.

Funds of a Licensee not invested in Small Concerns or in accordance with the last sentence of section 208(b) of the Act shall be deposited without delay in a bank insured by the Federal Deposit Insurance Corporation, or may be (a) invested in Time Certificates of Deposit maturing within one year or less, issued by any bank which is insured by the Federal Deposit Insurance Corporation, or (b) deposited in a savings account of such bank: Provided, however, That a Licensee may maintain a petty cash fund up to $500.

(Catalog of Federal Domestic Assistance Program 09.011 Small Business Investment Companies)


MITCHELL P. KOBELNICK, Administrator.

[FR Doc.76-26374 Filed 9-8-76; 8:45 am]

Miscellaneous Amendments

Correction

In FR Doc. 76-18573 appearing on page 2801 in the issue for Friday, June 25, 1976, in the brackets appearing under the heading for Part 112—Economic Oppo-
§ 121.3-7(a) of Part 121-SMALL BUSINESS SIZE STANDARDS

Size Standard Differential for Hawaii, the Virgin Islands, Puerto Rico, and Guam

On June 7, 1976, there was published in the Federal Register (41 FR 26202) a notice that the Small Business Administration proposed to adopt differentials applicable, in the case of size standards based on "dollars" to concerns that have 50 percent or more of their annual receipts attributable to business activity in Hawaii; the Virgin Islands, Puerto Rico, and Guam. A differential for Alaska has been in effect for several years.

The public was given an opportunity to comment on the proposal and no adverse comment was filed. Under the circumstances, we have decided to amend the regulation as proposed.

Accordingly, § 121.3-7(a) of Part 121, Chapter I, Title 13 of the Code of Federal Regulations is hereby revised to read as follows:

§ 121.3-7 Differentials.

(a) Alaska, Hawaii, and certain nonforeign areas outside the continental United States. In computing the annual receipts, average annual receipts, assets, net worth, or average net income of a concern (not including its affiliates) that has 50 percent or more of its annual receipts attributable to business activity within one of the States and nonforeign areas set forth above, the annual receipts, average annual receipts, assets, net worth, or average net income, shall be reduced by the percentage prescribed for such State or area.

<table>
<thead>
<tr>
<th>Percent</th>
<th>Alaska</th>
<th>Hawaii</th>
<th>Virgin Islands</th>
<th>Puerto Rico</th>
<th>Guam</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0</td>
<td>12.5</td>
<td>10.0</td>
<td></td>
<td>7.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Effective Date: This amendment shall become effective November 8, 1976, but, for the purpose of Government procurement, shall apply only to procurements for which invitations for bids or proposals are issued on or after November 8, 1976.

| Dated: August 31, 1976. |

MITCHELL P. KOBELINSKI, Administrator.

[F.R. Doc.76-26323 Filed 9-8-76; 8:45 am]

Title 16—Commercial Practices

CHAPTER 1—FEDERAL TRADE COMMISSION

[Docket No 9217]

PART 12—PROHIBITED TRADE PRACTICES, AND AFFIRMATIVE CORRECTIVE ACTIONS

Malco Hearing Instruments, Inc.

Subpart—Coercing and Intimidating: § 13.359 Distributors. Subpart—Commissioning or conspiring: § 13.388 To control allocations and soliation of customers. Subpart—Control of market practices and conditions: § 13.439 To enhance, maintain or unify prices. Subpart—To restrain or monopolize trade: § 13.470 To terminate or threaten to terminate competitors. Subpart—Cutting off supplies or service: § 13.580 Distributing or offering to distribute goods or service; § 13.585 Refusing to, or same terms and conditions; § 13.595 Threatening disciplinary action or otherwise. Subpart—Delaying or withholding corrections, adjustments or action: § 13.675 Delaying or withholding corrections, adjustments or action; § 13.677 Delaying or failing to deliver goods or provide service or facilities. Subpart—Maintaining resale prices: § 13.1150 Providing or requiring resale price maintenance; § 13.1155 Price schedules and announcement; § 13.1160 Penny short cuts. (Sec. 6, 38 Stat. 721; 15 U.S.C. 46. Interprets or applies sec. 5, 38 Stat. 719, as amended; 15 U.S.C. 45.)

In the Matter of Malco Hearing Instruments, Inc., a corporation.

Consent order entered December 15, Minneapolis, Minn., manufacturer of hearing aids, among other things to cease imposing on its dealers customer and territorial restrictions and exclusive dealing requirements. Malco, in 1973 and 1974, refused to sell to, or made available to, any person engaged in the repair of hearing aids, when, in the exercise of such right, that person made available to the public a price and discount terms available to all qualified dealers, and to maintain, for a ten-year period, a file record of any refusal to sell.

The order to cease and desist, including further order requiring report of compliance therewith, is as follows: 1

ORDER

1. Refusing to make available directly from it any of its products or materials to any dealer or person requesting a price and discount terms available directly from it any of its products or materials to any dealer or person requesting such terms.

2. Refusing to make available directly from it any of its products or materials to any dealer or person requesting such terms.

3. Refusing to make available directly from it any of its products or materials to any dealer or person requesting such terms.

4. Refusing to make available directly from it any of its products or materials to any dealer or person requesting such terms.
order of five (5) of Respondent's hearing aids on a cash with order basis.

3. Entering into, maintaining, preserving or soliciting orders by any method to sell or repair, setting of sales quotas or equivalent thereof, termination or threat thereof, request, report of sale, warranty limitation, use of names or addresses of a dealer's customers or other third persons as a basis or any arrangement of method of doing business which has the purpose or effect of restricting or limiting.

(a) For the time in which a dealer of Respondent's hearing aids advertise, offers for sale, sells or repairs such products, or

(b) The person or persons with whom a dealer of Respondent's hearing aids deals.

4. Failing to return any hearing aid submitted to Respondent for repair directly to the dealer who submitted such product for repair unless otherwise instructed in writing by such dealer.

5. Fixing, establishing, stabilizing, maintaining or suggesting the prices at which Respondent's hearing aids may be sold or advertised, offer for sale, or sell to the public, or a person repairing Respondent's hearing aid may repair such product, sold or advertised, however, that nothing in this Order shall prohibit Respondent, ten years from the date of entry of this Order from exercising any lawful rights it may then have under the Federal Trade Commission Act, 50 Stat. 633 (1937) and the McGuire Act, 66 Stat. 532 (1953) with respect to hearing aids, accessories or parts.

6. Requiring that a dealer participating in Respondent's cooperative advertising program not state or imply, in such cooperative advertisements, that the dealer also deals in other brands of hearing aids, which file must contain a record of a communication to such dealers or persons on whom it has served a copy of Appendix A, and a copy of the publication which includes Respondent's advertisement required by this Order.

(c) Within Sixty (60) days after service upon it of this Order, file with the Commission a report, in writing, setting forth in detail the manner and form in which it has complied with this Order and a list of all dealers and other persons on whom it has served a copy of Appendix A, and a copy of the publication which includes Respondent's advertisement required by this Order.

(d) For a period of Ten (10) years from the date hereof establish and maintain a file of all records referring or relating to Respondent's refusal to sell any hearing aid dealer, or person engaged in the business of repairing hearing aids, which file must contain a record of a communication to such dealers or persons on whom it has served a copy of Appendix A, and a copy of the publication which includes Respondent's advertisement required by this Order.

3. Failing to include and deliver with any of Respondent's hearing aids sold by Respondent any express product warranty for such product as provided by Respondent to the user.

It is further ordered, that Respondent shall:

(a) Forthwith distribute a copy of this Order to each of its operating units, to its present corporate officers and to its present sales and repair personnel, and shall secure from each such officer, employee or other person, a signed statement acknowledging receipt of said Order;

(b) Within Thirty (30) days after service upon it of this Order, distribute a copy of the letter attached to this Order and made a part hereof as Appendix A to each of its existing hearing aid dealers and to any other person to whom it was engaged in the business of repairing Respondent's products;

(c) Within Sixty (60) days after service upon it of this Order, file with the Commission a report, in writing, setting forth in detail the manner and form in which it has complied with this Order, of the refusal, and the date of the refusal.

§ 253.133 Tropical differential.

§ 253.134 Penalties.

Title 35—Panama Canal

CHAPTER 1—CANAL ZONE REGULATIONS

PART 253—REGULATIONS OF THE SECRETARY OF THE ARMY

Subpart D—Compensation and Allowances

Tropical Differential

The purpose of this amendment is to authorize payment of a tropical differential to the United States citizen employees who, pursuant to a legal separation, is living apart from his or her spouse and who otherwise would be precluded by the regulations from receiving it.

In 35 CFR Part 253, § 253.133 is amended by adding a new paragraph (d) reading as follows:

§ 253.133 Tropical differential.

Title 36—Parks, Forests, and Public Property

CHAPTER II—FOREST SERVICE, DEPARTMENT OF AGRICULTURE

Grazing on National Forests and National Grasslands

On May 27, 1976, a document was published in the Federal Register (41 FR 21644) proposing to amend the regulations at 35 CFR Part 253, concerning grazing on the National Forests and National Grasslands.

Interested parties were given 30 days to make written submissions regarding the proposed rulemaking. On June 25, 1976, the period for comment was extended to July 28, 1976 (41 FR 26578). The written comments filed in response to the notice of proposed rulemaking have been carefully considered. Based on these comments, the clarification, modifications, and revisions explained below have been made in the final rule document.

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
§ 231.5 [Removed]

2. Section 231.5, Grouping of the National Grasslands into administrative units and providing specific designations therefor is revoked.

PART 231—GRAZING

3. Paragraph (b) (1) of § 231.1 is revised to read as follows:

§ 231.1 Range resource development

(a) and administration.

(b) Definitions. (1) "National Forest System lands," as used in this part, are the National Forests, National Grasslands, Land Utilization Projects, and other Federal lands for which the Forest Service has administrative jurisdiction.

4. Section 231.2 is retitled and is revised to read as follows:

§ 231.2 Range planning and management.

(a) Range allotments will be designated on National Forest System lands and on other lands under Forest Service control. Associated private and other public lands should, with concurrence of the landowner, be considered in such designations to form logical range management units.

(b) Each range allotment and wild horse or burro territory will be initially analyzed and a plan of management developed and implemented. The analysis and plans will be updated whenever needed as determined by conditions on the allotment or territory.

5. Paragraph (d) of § 231.3 is amended to read as follows:

§ 231.3 Grazing permits and grazing agreements.

(d) Grazing permits and grazing agreements authorizing livestock use on National Forest System lands and on other lands under Forest Service control shall be as follows:

(1) Paid term permits may be issued for periods of 10 years or less to persons who own the livestock to be grazed and such base ranch property as the Chief, Forest Service, may require. Term permits will be issued to expire December 31 of the mid-year of the decade (1985, 1995, etc.). Term permits may also be issued in connection with changes of ownership of the base property or the permitted livestock of term permittees. Term permits are renewable at the end of each term period provided the provisions and requirements under which they are issued continue to be met. The term permit provides its holder first priority for its renewal at the expiration of the term permit period. The Chief, Forest Service, shall prescribe provisions and requirements under which term permits may be issued, renewed, and administered, including:

(i) Criteria for eligibility;

(ii) Ownership of base property and livestock;

(iii) Specifications for ownership of base property;

(iv) Acquisition of base property and/or permitted livestock;

(v) Conditions for the approval of nonuse of permit for specified periods;

(vi) Upper limits governing size of permit that any person, firm or corporation may hold;

(vii) Conditions whereby waiver of grazing privileges may be confirmed and new applicants recognized.

(b) Paid temporary permits may be issued annually to persons under such provisions and requirements as the Chief, Forest Service, shall prescribe.

(c) Paid term or temporary permits with a specific on-and-off provision may be issued to persons owning livestock that will graze on ranges only part of which is National Forest System land and on other lands under Forest Service control.

(f) Free permits may be issued to:

(i) Persons who reside on ranch or agricultural lands within or contiguous to National Forest System lands for not to exceed 10 head of livestock owned or kept for domestic purposes and whose products are consumed or whose services are used directly by the family of the resident, and who distinctly need such National Forest System lands to support such domestic animals.

(ii) Persons who clearly need National Forest System lands to support the number of horses, mules or burros needed to manage permitted livestock.

(iii) Prospectors, campers, and travelers for the few head of livestock actually using the land during the period of occupancy.

(iv) Others as may be authorized by the Chief, Forest Service.

6. Paragraph (a) of § 231.5 is amended by adding a paragraph (10):

§ 231.5 Fees, payments, and refunds or credits.

(a) * * *

(10) For negotiated permits, fees paid will be a negotiated item. It may be more or less than standard fees.

(b) * * *

§ 231.6 Revocation and suspension of grazing permits.

The Chief, Forest Service and Regional Foresters are authorized to revoke or suspend in whole or in part, Forest Service grazing permits or temporarily suspend the use of such permit on the following ground:

(a) Criterion for eligibility;

(b) Ownership of base property and livestock;

(c) Specifications for ownership of base property;

(d) Acquisition of base property and/or permitted livestock;

(e) Conditions for the approval of nonuse of permit for specified periods;

(f) Upper limits governing size of permit that any person, firm or corporation may hold;

(g) Conditions whereby waiver of grazing privileges may be confirmed and new applicants recognized.

(h) Paid temporary permits may be issued annually to persons under such provisions and requirements as the Chief, Forest Service, shall prescribe.

(i) Paid term or temporary permits with a specific on-and-off provision may be issued to persons owning livestock that will graze on ranges only part of which is National Forest System land and on other lands under Forest Service control.

(j) Free permits may be issued to:

(i) Persons who reside on ranch or agricultural lands within or contiguous to National Forest System lands for not to exceed 10 head of livestock owned or kept for domestic purposes and whose products are consumed or whose services are used directly by the family of the resident, and who distinctly need such National Forest System lands to support such domestic animals.

(ii) Persons who clearly need National Forest System lands to support the number of horses, mules or burros needed to manage permitted livestock.

(iii) Prospectors, campers, and travelers for the few head of livestock actually using the land during the period of occupancy.

(iv) Others as may be authorized by the Chief, Forest Service.

(k) * * *

(9) Negotiated permits may be issued in the absence of applicants qualified for other permits or agreements for periods up to 5 years. Authorized use will be under a grazing management plan.

(l) * * *

* 64 Stat. 88 (16 U.S.C. 580 1)

7. Section 231.6 is revised to read as follows:

§ 231.6 Revocation and suspension of grazing permits.

The Chief, Forest Service and Regional Foresters are authorized to revoke or suspend in whole or in part, Forest Service grazing permits or temporarily suspend the use of such permit on the following ground:

(a) Criterion for eligibility;

(b) Ownership of base property and livestock;

(c) Specifications for ownership of base property;

(d) Acquisition of base property and/or permitted livestock;

(e) Conditions for the approval of nonuse of permit for specified periods;

(f) Upper limits governing size of permit that any person, firm or corporation may hold;

(g) Conditions whereby waiver of grazing privileges may be confirmed and new applicants recognized.

(h) Paid temporary permits may be issued annually to persons under such provisions and requirements as the Chief, Forest Service, shall prescribe.

(i) Paid term or temporary permits with a specific on-and-off provision may be issued to persons owning livestock that will graze on ranges only part of which is National Forest System land and on other lands under Forest Service control.

(j) Free permits may be issued to:

(i) Persons who reside on ranch or agricultural lands within or contiguous to National Forest System lands for not to exceed 10 head of livestock owned or kept for domestic purposes and whose products are consumed or whose services are used directly by the family of the resident, and who distinctly need such National Forest System lands to support such domestic animals.

(ii) Persons who clearly need National Forest System lands to support the number of horses, mules or burros needed to manage permitted livestock.

(iii) Prospectors, campers, and travelers for the few head of livestock actually using the land during the period of occupancy.

(iv) Others as may be authorized by the Chief, Forest Service.

(k) * * *

(9) Negotiated permits may be issued in the absence of applicants qualified for other permits or agreements for periods up to 5 years. Authorized use will be under a grazing management plan.

(l) * * *

* 64 Stat. 88 (16 U.S.C. 580 1)
The permittee does not comply with the provisions and requirements in the grazing permit, the regulations of the Secretary of Agriculture on which the permit is based, and instructions issued by Forest officers; and

(b) The permittee knowingly and willfully makes a false statement or representation in the grazing application or amendment thereto; or

(c) The permittee violates or does not comply with, Federal laws or regulations or State laws relating to protection of air, water, fish, wildlife, and other environmental values when exercising the grazing use authorized by the permit.

8. Section 231.7 is amended to read as follows:

§ 231.7 Cooperation in management.

(a) Cooperation with local livestock organizations. (1) Authority. The Chief, Forest Service, is authorized to recognize, cooperate with, and assist local livestock associations in the management of the livestock and range resources on a single range allotment, associated groups of allotments or on-控 land on which the members’ livestock are permitted to graze.

(2) * * *

(iv) Share costs for handling of livestock, construction and maintenance of range improvements or other accepted programs deemed needed for proper management of the permitted livestock and range resources.

(b) Cooperation with national, State, and county livestock organizations. The policies and programs of National, State, and county livestock organizations give direction to, and reflect in, the practices of their members. Good working relationships with these groups is conducive to the betterment of range management on both public and private lands. The Chief, Forest Service, will endeavor to establish and maintain close working relationships with National livestock organizations having an interest in the administration of National Forest System lands, and direct Forest officers to work cooperatively with State and county livestock organizations having similar interests.

(c) Interagency cooperation. The Chief, Forest Service, will cooperate with other Federal agencies interested in improving range management on public and private lands.

(d) Cooperation with others. The Chief, Forest Service, will cooperate with other agencies, institutions, organizations, and individuals who have an interest in the improvement of range management on public and private lands.

9. Paragraph (a) of §231.8 is revised to read as follows:

§ 231.8 Cooperation in control of estray or unbranded livestock, animal diseases, noxious farm weeds, and use of pesticides.

(a) Insofar as it involves National Forest System lands and other lands under Forest Service control or the livestock which graze thereon, the Chief, Forest Service, will cooperate with:

(1) State, county, and Federal agencies in the application and enforcement of all laws and regulations relating to livestock diseases, sanitation and noxious farm weeds;

(2) The Animal Health Inspection Service and other Federal and/or State Agencies and institutions in surveillance of pesticide spray programs; and

(3) State cattle and sheep sanitary or brand boards in control of estray and unbranded livestock to the extent it does not conflict with the Wild Free-Roaming Horses and Burros Act of December 15, 1971.


10. Section 231.9 is amended to read as follows:

§ 231.9 Range improvements.

(a) The Chief, Forest Service, is authorized to install and maintain structural and nonstructural range improvements needed to manage the range resources on National Forest System lands and other lands controlled by the Forest Service.

(b) Such improvements may be installed and maintained by individuals, organizations or agencies other than the Forest Service subject to the following:

(1) All improvements must be authorized by cooperative agreement, memorandum of understanding or special use permit.

(2) * * *

(c) A user of the range resource on National Forest System lands and other lands under Forest Service control may be required by the Chief, Forest Service, to maintain such improvements in a satisfactory state of repair.

(82 Stat. 427 (16 U.S.C. 550h))

PART 261—TRESPASS

11. Section 261.13 is amended and paragraph (g) is added to read as follows:

§ 261.13 Impoundment and disposal of unauthorized livestock.

Unauthorized livestock on the National Forest System lands and on other lots under Forest Service control, which are not removed from the area within the periods prescribed by this regulation, may be impounded and disposed of by a Forest officer as provided herein.

(a) When a Forest officer determines unauthorized livestock is occurring and has definite knowledge of the kind of unauthorized livestock, and knows the name of the owners, such livestock may be impounded any time 5 days after written notice of intent to impound unauthorized livestock is mailed to certified or registered mail or personally delivered to such owner.

(b) When a Forest officer determines that unauthorized livestock use is occurring but does not have complete knowledge of the kind of livestock, or if the name of the owners thereof are unknown, such livestock may be impounded not later than 15 days after the date a notice of intent to impound unauthorized livestock is first published in a local newspaper and posted at the county courthouse and in one or more local post offices. The notice will identify the area or areas in which it will be effective.

(c) Unauthorized livestock on National Forest System lands and on other lands under Forest Service control, which are owned by persons given notice under paragraph (a) of this section, and any unauthorized livestock in areas for which a notice has been posted and published under paragraph (b) of this section, may be impounded without further notice any time within the 12-month period immediately following the effective date of the notice or notices given under paragraphs (a) and (b) of this section.

(d) Following the impoundment of unauthorized livestock, a notice of sale of impounded livestock will be published in a local newspaper, and posted at the county courthouse and in one or more local post offices. The notice will describe the livestock and specify the date, time, and place of sale. The date set shall be at least 5 days after the publication and posting of such notices.

(e) The owner may redeem the livestock any time before the date and time set for the sale by submitting proof of ownership and paying for all expenses incurred by the United States in cleaning, impounding, and feeding or pasturing the livestock. However, when the impoundment costs exceed fair market value, a minimum acceptable redemption price at fair market value may be established for each head of livestock.

(f) If the livestock are not redeemed on or before the date and time fixed for their sale, they shall be sold at public sale to the highest bidder, providing his bid is at or above the minimum amount set by the Forest Service. If a bid at or above the minimum amount is not received, the livestock may be sold at private sale at or above the minimum amount, reoffered at public sale, condemned and destroyed, or otherwise disposed of. When livestock are sold pursuant to this regulation, the Forest officer making the sale shall furnish the purchaser a bill of sale or other written instrument evidencing the sale. Agreements may be made with State agencies whereby unbranded livestock or livestock of unknown ownership are released to the agency for disposition in accordance with State law.

(g) The term livestock as used in this section refers to cattle, sheep, goats, hogs, and equines not meeting the definition of wild, free-roaming horses or burros in 36 CFR 231.11(a)(2).


Effective date: These provisions shall take effect on September 9, 1976.
RULES AND REGULATIONS

CHAPTER 1—U.S. POSTAL SERVICE

PART 111—GENERAL INFORMATION ON POSTAL SERVICE

Reimbursement for Official Mail Service

On June 18, 1976, the Postal Service published in the Federal Register (41 FR 24726) a notice of proposed rulemaking on this subject, setting forth a proposed change in §137.21 of the Postal Service Manual. The proposed change is designed to reflect more accurately the scope of the statutory provisions concerning the collection of postage and fees for official mail service provided to executive and judicial officers of the U.S. Government. Thus, the proposed regulation explicitly recognizes the broad authority of the Postal Service to obtain adequate reimbursement for official mail service, and indicates that the Assistant General Counsel of the Government Accounting and Examination Branch, Finance Department, of the Postal Service may require the use of postage meters, or other forms of positive accountability, where in his judgment such measures are necessary to secure adequate reimbursement.

Interested persons were invited to submit written data, views, or arguments concerning the proposed regulation. Upon request the initial comment period was extended two weeks (41 FR 26545).

Three comments were received. One commenter expressed the concern of Federal agencies over the potential high cost to agencies if postage meters were required to be used. He said that, prior to implementing any such requirement, agency management officials would need to be assured that alternative actions had been considered and that the selected action has the best cost/benefit ratio. Another commenter requested that an adequate advance notice be given to agencies of any major change in the method of official mail accountability. The third commenter expressed the fear that the use of postage meters would delay dispatch of mail because he believes that neither Congress nor the Office of Management and Budget would authorize additional personnel to handle the increased workload which he believes may result.

In our opinion, the comments generally suggest considerations and a reasonable modus operandi which we would have considered and adopted in the administration of this provision. However, in order to allay any fears we are amending the new regulation to make these suggestions explicit.

In view of the considerations discussed above, the Postal Service hereby adopts, as amended, the following amendment of the Postal Service Manual, effective immediately:

Section 137.21 of the Postal Service Manual is revised to read as follows:

§137.21. Collection of postage and fees—Departments, agencies, and establishments of the United States Government must reimburse the Postal Service the equivalent amount of postage and fees due for the official mail service they receive. Instructions governing the manner of reimbursement for official mail service are issued and administered by the Manager, Government Revenue and Examination Branch, Finance Department of the Postal Service. Federal Government offices and officers must promptly furnish, in the manner and form requested, all information the Manager considers necessary to assure the accuracy of measurements of official mail use and the adequacy of budgeting to facilitate timely payment. The Manager may require offices and officers to establish improved methods of estimating or measuring official mail volume, or to initiate the use of postage meters or other forms of positive accountability for the use of official mail services, where he determines such action is necessary to secure adequate reimbursement to the Postal Service. Prior to making such determination the Manager will consult with the office or officer involved as to possible alternative actions that might be taken which would be effective but which might have a better cost/benefit ratio. If the Manager, nevertheless, decides to require the use of postage meters or other forms of positive accountability for the use of official mail services, adequate advance notice will be given to affected agencies.

A Post Office Service (Domestic) transmittal letter making these changes in the pages of the Postal Service Manual will be published and will be transmitted to subscribers automatically. These changes will be published in the Federal Register as provided in 39 CFR 111.3.

(39 U.S.C. 401, 3206, 3209)

W. Allen Sanders,
Assistant General Counsel.

[FR Doc.76-23930 Filed 9-9-76; 8:45 am]

Title 40—Protection of Environment

CHAPTER 1—ENVIRONMENTAL PROTECTION AGENCY

SUBCHAPTER I—AIR PROGRAMS

PART 52—APPROVAL AND PROMULGATION OF IMPLEMENTATION PLANS

Notice of Correction

On February 13, 1976, EPA published in the Federal Register (41 FR 6785) approval of regulations for review of indirect sources in the State of Connecticut. In that approval notice 40 CFR §§52.375, Review of New Sources and Modifications, was deleted. However, the section number, 52.375, was wrong and is hereby being corrected. The number 52.381 should have been deleted rather than the number 52.375. Therefore, Subpart H of Chapter I, Title 40, Part 52 of the Code of Federal Regulations is corrected as follows:

§52.381 [Deleted]

Section 52.381. Review of New Sources and Modifications is deleted.

Dated: September 2, 1976.

Roger Sterlow,
Assistant Administrator for Air and Waste Management.

[FR Doc.76-26283 Filed 9-9-76; 8:45 am]

Title 41—Public Contracts and Property Management

CHAPTER 1—FEDERAL PROCUREMENT REGULATIONS

[FPFR Amdt. 160]

PART 1—GENERAL

Subpart 1-1.3—General Policies

OPPORS BY FEMALE ENTERPRISES

This amendment of the Federal Procurement Regulations (FPFR) changes §1-1.302, Procurement sources, with respect to the solicitation of offers. The Special Assistant to the President for Women's Affairs has expressed the view that procurement regulations need to be revised to ensure that female enterprises are not discriminated against during the solicitation process. The amendment requires that offers shall not knowingly be solicited on the basis of race, creed, color, sex, age, or national origin.

Section 1-1.302-1 is amended to change paragraph (b), as follows:

§1-1.302-1 General.

(b) Irrespective of whether the procurement of supplies or services from sources outside the Government is to be effected by formal advertising or by negotiation, competitive offers ("bids" in the case of procurement by formal advertising, "proposals" in the case of procurement by negotiation) shall be solicited from all such qualified sources as are deemed necessary by the contracting officer to ensure such full and free competition as is consistent with the procurement of types of supplies and services necessary to meet the requirements of the agency concerned. Offers shall not knowingly be solicited on the basis of race, creed, color, sex, age, or national origin of prospective sources.

Effective date: This amendment is effective October 26, 1976.

Dated: September 2, 1976.

Jack Eckerd,
Administrator of General Services.

[FR Doc.76-26534 Filed 9-8-76; 8:45 am]
CHAPTER 101—FEDERAL PROPERTY MANAGEMENT REGULATIONS

SUBCHAPTER H—UTILIZATION AND DISPOSAL

[FFAR Amendment H-08] PART 101-46—UTILIZATION AND DISPOSAL OF PERSONAL PROPERTY PURSUANT TO EXCHANGE/SALE AUTHORITY Subpart 101-46.4—Disposal

Availability of Proceeds of Sale

This regulation provides updated references to title 7 of the General Accounting Office Policy and Procedures Manual for Guidance of Federal Agencies. Section 101-46.404 is amended as follows:

§ 101-46.404 Availability of proceeds of sale.

Except as otherwise authorized by law, proceeds from sales of personal property disposed of pursuant to this Subpart 101-46.4 shall be accounted for in accordance with General Accounting Office Policy and Procedures Manual for Guidance of Federal Agencies, Title 7, Fiscal Procedures, section 15.4. The requirements for a written administrative determination to establish that a bona fide replacement is involved are set forth in § 101-46.202(a)(4). Procedures for the application of the proceeds from sale for the acquisition of similar items follow:

(a) Sale of property before the purchase of replacement property. (1) When the property to be replaced is sold before the acquisition of the replacement property, the proceeds of such sales will be credited to the agency's budget clearing account.

(2) * * *

(3) When the acquisition of the replacement property is subsequently made and the obligation incurred, Standard Form 1061, Voucher and Schedule of Withdrawals and Credits, or other approved form should be processed to charge the budget clearing account. * * * F3875*.*

(2) * * *

(3) * * *

(4) * * *

Sec. 205(o) [49 Stat. 390; 49 U.S.C. 495(o)]

Effective date. This regulation is effective September 3, 1976.

It is hereby certified that the impact does not meet the Inflation Impact criteria for major rules or regulations.

Dated: August 30, 1976.

JACK ECKERT,
Administrator of General Services.

[FR Doc.76-26291 Filed 9-8-76; 8:45 am]

RULES AND REGULATIONS

Title 46—Shipping

CHAPTER I—COAST GUARD, DEPARTMENT OF TRANSPORTATION

[Docket No. MT-134; Amdt. No. 145-I]

PART 146—TRANSPORTATION OR STORAGE OF MILITARY EXPLOSIVES ON BOARD VESSELS

Authority Citations

For reasons set forth in a document amending the authority citations in Parts 171-179 of title 49, Code of Federal Regulations, appearing elsewhere in this issue of the Federal Register, 49 CFR Part 146 is amended by adding an authority citation immediately following the table of contents to read as follows:

* * * * * * * * * * *

Authority


Effective date. This amendment is effective on January 3, 1977.

Issued in Washington, D.C., on August 31, 1976.

James T. Curtis, Jr.,
Director, Materials Transportation Bureau.

[FR Doc.76-26377 Filed 9-8-76; 8:45 am]

Title 47—Telecommunication

CHAPTER I—FEDERAL COMMUNICATIONS COMMISSION

[FCC 76-620]

PART 0—COMMISSION ORGANIZATION

Review Board

Adopted: August 31, 1976.

Released: September 3, 1976.

By the Commission: 1. Section 0.361 (f) of the rules provides that a minimum of three members will participate in each "case" referred to the Review Board. While it is relatively clear that the term "case" refers to the review of initial decisions only, and not to interlocutory matters, it is desirable that the provision be clarified. Action on urgent interlocutory matters (e.g., moltons for extension of time) should not be deferred if less than three Board members are available to act. We are therefore amending the first sentence of § 0.361(f) to read as follows:

(f) * * *

(1) Except for interlocutory matters, a minimum of three members will participate in each matter referred to the Board. * * *

2. Accordingly, it is ordered, effective September 15, 1976, That § 0.361 is amended as set out below. Authority for the amendment is set out in sections 4 (i) and (j), 5(d) and 303(f) of the Communications Act of 1934, as amended, 47 U.S.C. 154 (i) and (j), 155(d) and 303 (c). Because the amendment involves a matter of procedure and merely clarifies an existing provision, the prior notice and effective date provisions of 5 U.S.C. 553 are inapplicable.


FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

In Part 0 of Chapter I of Title 47 of the Code of Federal Regulations, § 0.361 (f) is revised to read as follows:

§ 0.361 General authority.

* * * * * * * *

(1) Except for interlocutory matters, a minimum of three members will participate in each matter referred to the Board. A majority of the members who participate in a case shall constitute a quorum. Any member assigned to a case who is not present at oral argument may, after reading the transcript of oral argument, participate in the Board's decision. However, so far as practicable, all of the members of the Board assigned to a case shall hear oral argument.

[FR Doc.76-26361 Filed 9-8-76; 8:45 am]

Title 49—Transportation

SUBTITLE B—OTHER REGULATIONS RELATING TO TRANSPORTATION

CHAPTER I—MATERIALS TRANSPORTATION BUREAU, DEPARTMENT OF TRANSPORTATION

[Docket No. MT-138; Amdt. No. 107-3]

PART 107—PROCEDURES

Presumption and Enforcement Procedures

The purpose of these amendments to 49 CFR Part 107 is to (1) establish procedural regulations that implement the preemption provisions of section 112 of the Hazardous Materials Transportation Act (Title I of Pub. L. 93-633), (2) prescribe procedures to be followed by the Materials Transportation Bureau (MTB) in carrying out its enforcement responsibilities under sections 109, 110, and 111 of the same Act, and (3) add several general procedural provisions covering the MTB's hazardous materials public dockets, service of documents and subpoenas.

AMENDMENTS TO GENERAL PROVISIONS

The list of definitions in § 107.3 is expanded to include a definition of "person" which covers all of the commonly recognized classes of legal entities regularly doing business, as well as individuals. A definition of "respondent" is added for use in connection with the new Subpart D enforcement procedures. A definition of "State" is being incorporated verbatim from section 103(f) of the Hazardous Materials Transportation Act.

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
A new § 107.9 is added setting forth a general description of the materials available for transporting in the MTB's hazardous materials public docket room.

A new § 107.11 prescribes the means for effecting service of documents for purposes of any of the various hazardous material procedural regulations.

A new § 107.13 specifies who has authority to issue subpoenas under section 109(a) of the Hazardous Materials Transportation Act and prescribes the procedures for their issuance and service, the payment of witness fees, the handling of motions to quash or modify, and their enforcement.

Section 107.215 invites States and political subdivisions (not private parties) to submit applications for determination of preemption.

Section 107.217 requires a State or political subdivision applying for a preemption determination to provide all information that application on those persons which the State or political subdivision can reasonably identify as being affected by the requested determination.

The OHMO may add to the above list or publish notice in the Federal Register, or both. All persons upon whom notice is served or who are identified in the Federal Register notice will have the opportunity to submit written comments. Under § 107.219, as in the case of inconsistency rulings, the Director, OHMO, has broad procedural authority to fully develop the necessary information for making his determination. This includes the authority to require supplemental submissions from the applicant. The Director must receive notice if there is insufficient information to make his determination; if the applicant fails to provide requested additional information or the supplement, the Director will provide notice to affected persons. The Director will only consider a request for a preemption determination if the inconsistency of the State or political subdivision in issue has been affirmatively fixed by the order of a court of competent jurisdiction by a § 107.229 administrative ruling that has become final, or through the express acknowledgment of inconsistency by the applicant. When the OHMO has received all of the necessary information for reaching a determination, all participants are so notified and, if a formal determination is not issued within 90 days, § 107.232 affords the applicant the same opportunity for appeal as the case of a denial. Section 107.233, which provides for the issuance of a written determination, specifies the principal factors considered by the Director, OHMO, in reaching that determination. Whether a State's or political subdivision requirement unreasonably burdens commerce is a question of fact and requires a balancing of the State's or political subdivision's interest in public health and safety against the national interest in maintaining a free flow of commerce. The factors listed in § 107.233(b), no single one of which is dispositive, are in determining whether a State or political subdivision requirement creates an unreasonable burden, provide in combination the test by which that determination is reached. Some of the factors employed by the Supreme Court in deciding whether various State transportation safety requirements impose an unreasonable burden on commerce, e.g., South Carolina State Highway Department v. Barnwell, 303 U.S. 177 (1938); Southern Pacific v. Arizona, 325 U.S. 761 (1945); Bibb v.
probable violation with the respondent having forth the procedures applicable to the

lation indicating that the OHMO is con-

spondent with options as to the degree of

raise.

In a situation where they consider

pending violation poses a risk requiring corrective steps he taken for the protec-

tion of public health and safety without
delay, an order directing immediate com-

pliance can be issued under § 107.319. Al-

tough prior notice and opportunity for

a hearing procedure do not apply in such

situations, the order is subject to admin-

ister appeal.

Section 107.331 and 107.333 reflect gen-

erally the authority contained in section 111 (a) and (b), respectively, of the Haz-

ardous Materials Transportation Act. These provisions provide for injunctive

relief and punitive damages for violations of the hazardous materials regulations

and for the enforcement of compliance orders. When time permits the Depart-

ment of Justice will bring an action on behalf of the MTB in the appropriate U.S.

District Court. However, when the situation involves an imminent hazard

MTB may bring the action on its own motion in the appropriate U.S. District Court.

When a respondent receives a notice of probable violation indicating that the

Director, OHMO, is considering assessing a civil penalty, the respondent may, in-

within 30 days of service, (1) pay the amount of the preliminary assessment, (2) make

an informal response denying the allegations in whole or in part and offering ex-

planatory information, or (3) request a hearing. The filing of an informal re-

response provides the opportunity for an informal conference and possible compro-

mise of the case. If a hearing is requested it will be conducted before an OHMO

official who may dismiss the case or issue an order assessing a civil penalty. His or

her order may be appealed within 20 days after service. In any case in which a civil

penalty is assessed, the factors listed in § 107.355 are considered.

At any time after the issuance of a no-

ice of probable violation in a civil penalty

case and before it is referred to the De-

partment of Justice for collection, the civil penalty can be compromised and set-

tied by payment of the amount agreed

upon in compromise.

Section 107.371 reflects the criminal

penalty provided for in section 110 of the

Hazardous Materials Transportation Act. Section 107.373 describes generally the

procedures followed by the OHMO and the MTB with respect to possible criminal

violations.

Since these amendments relate to prac-

tices and procedures of the MTB and its

Office of Hazardous Materials Operations, notice and public procedure thereon is

not necessary. However, these amendments are intimately related to actions being

taken in Docket HM-134 appearing elsewhere in this edition of the FED-

ERAL REGISTER, these amendments are

handed by the provisions of new Subparts C and D of 49 CFR Part 107 to the Docket Sec-

tion, Materials Transportation Bureau, U.S. Department of Transportation, Trans

Point Building, Washington, D.C. 20590. All comments received before the close of business on June 1, 1977, will be

considered during the review, and will be available in the docket for examination,

both before and after that date.

To be given particular attention during

the review will be the civil penalty hear-

ing procedures set forth in § 107.353

which the Bureau recognizes may be

more formal and burdensome than nec-

essary to fulfill the statutory required "opportunity for hearing". Accordingly,

the Bureau is particularly desirous of

receiving comments with respect to this

specific subject.

In consideration of the foregoing, 49

CFR Part 107 is amended as follows:

a. adding the following new section numbers

and headings:

Subpart A—General

Provisions

Sec.

107.1

Public docket room.

107.11

Service.

107.12

Subpoena; witness fees.

107.13

Subpart C—Preemption

107.201

Purpose and scope.

107.202

Inconsistency

107.203

Application.

107.204

Notice.

107.205

Proceeding.

107.206

Ruling.

107.207

Appeal.

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2. The authority citation following the table of sections is revised as follows:


3. 49 CFR 107.3 is amended by adding new definitions of "Act," "Person," "Respondent," and "State" as amended reads as follows:

§ 107.3 Definitions.

As used in this part:


"OHMO" means the Office of Hazardous Materials Operations.

"MTB" means the Materials Transportation Bureau.

"Person" includes a corporation, company, association, firm, partnership, society, and joint stock company, joint venture, sole proprietorship, as well as any officer, director, owner or duly authorized representative of any such unit or an individual.

"Respondent" means a person upon whom the OHMO has served a notice of probable violation.

"State" means a State of the United States, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, American Samoa, or Guam.

4. Subpart A is amended by adding new §§ 107.11, 107.13 immediately following § 107.7 to read as follows:

§ 107.9 Public docket room.

There is established in the MTB offices at 2100 2nd Street, SW., Washington, D.C., a public docket room in which there is available for public inspection and copying:

(a) Copies of notices of proposed rulemaking issued by the OHMO or its predecessor agency, including advance notices, together with the comments received thereon and the following rulemaking proceedings, copies of any related Federal Register notices, final rules, petitions for reconsideration, and decisions issued in response to petitions for reconsideration;

(b) Applications for exemptions from the Department of Transportation's regulations governing the transportation of hazardous materials, including supporting data, memoranda of any informal meetings with applicants, related Federal Register notices, comments received thereon during the public comment period and copies of decisions issued granting or denying applications for exemptions or modified exemptions;

(c) Applications for inconsistency rulings and nonpreemption determinations under Subpart G of this part, together with the written materials received thereon, related documents filed with the MTB, copies of related Federal Register notices, and rulings, determinations and orders issued in response to such applications;

(d) Records of compliance order proceedings and copies of OHMO compliance orders;

(e) Appeals filed under this part and MTB decisions issued in response to those appeals; and

(f) Such other information pertaining to the MTB's hazardous materials program required by statute to be made available for public inspection and copying and any information which the MTB or OHMO determines should be made available to the public.

§ 107.11 Service.

(a) Each order, notice, or other document required to be served under this part shall be served personally or by registered or certified mail, except as otherwise provided.

(b) Service upon a person's duly authorized representative constitutes service upon that person.

(c) Service by registered or certified mail is complete upon mailing. An official certificate of service shall be signed by the person at whose last known address served, or by his authorized representative.

§ 107.13 Subpoenas; witness fees.

(a) The Director, MTB, the Assistant General Counsel for Materials Transportation Law, or the MTB official designated immediately following Appendix B to the CFR shall serve a subpoena in the manner described therein. The Director, MTB, or the designated MTB official who issued the subpoena determines the presence of the subpoenaed witness will materially advance the proceeding;

(b) A subpoena may require the attendance of a witness, or the production of documentary or other tangible evidence in the possession or under the control of the person served, or both.

(c) A subpoena may be served personally by any person who is not an interested person.

(d) A subpoena may be served personally by any person who is not an interested person.

(e) A subpoena may be served personally by any person who is not an interested person.

(f) A subpoena may be served personally by any person who is not an interested person.

(g) A subpoena may be served personally by any person who is not an interested person.

(h) A subpoena may be served personally by any person who is not an interested person.

(i) A subpoena may be served personally by any person who is not an interested person.

(j) A subpoena may be served personally by any person who is not an interested person.

(k) A subpoena may be served personally by any person who is not an interested person.

(l) A subpoena may be served personally by any person who is not an interested person.

(m) A subpoena may be served personally by any person who is not an interested person.

(n) A subpoena may be served personally by any person who is not an interested person.

(o) A subpoena may be served personally by any person who is not an interested person.

(p) A subpoena may be served personally by any person who is not an interested person.

(q) A subpoena may be served personally by any person who is not an interested person.

(r) A subpoena may be served personally by any person who is not an interested person.

(s) A subpoena may be served personally by any person who is not an interested person.

(t) A subpoena may be served personally by any person who is not an interested person.

(u) A subpoena may be served personally by any person who is not an interested person.

(v) A subpoena may be served personally by any person who is not an interested person.

(w) A subpoena may be served personally by any person who is not an interested person.

(x) A subpoena may be served personally by any person who is not an interested person.

(y) A subpoena may be served personally by any person who is not an interested person.

(z) A subpoena may be served personally by any person who is not an interested person.

1. The original subpoena hearing a certificate of service shall be filed with the MTB official having responsibility for the proceeding in connection with which the subpoena was issued.

2. A witness subpoenaed by the MTB shall be paid the same fees and mileage as would be paid to a witness in a proceeding in the district courts of the United States. The witness fees and mileage shall be paid by the person at whose instance the subpoena was issued.

3. Notwithstanding the provisions of paragraph (a) of this section, and upon request, the witness fees and mileage may be paid by the MTB if the MTB official who issued the subpoena determines on the basis of good cause shown, that:

(a) The presence of the subpoenaed witness will materially advance the proceeding;

(b) The person at whose instance the subpoena was issued would suffer a serious hardship if required to pay the witness fees and mileage.

(c) Any person to whom a subpoena is directed may, prior to the time specified therein for compliance, but in no event more than 10 days after the date of service of such subpoena, apply to the designated MTB official who issued the subpoena, or if he is unavailable, to the Director, MTB, for a conditional modification of the subpoena. The application shall contain a brief statement of the reasons relied upon in support of the action sought therein. The Director, MTB, or the designated MTB official, as the case may be, may:

(d) Deny the application;

(e) Quash or modify the subpoena;

(f) Condition denial of the application to quash or modify the subpoena upon the satisfaction of certain just and reasonable requirements. The denial may be summary.

(g) If there is a refusal to obey a subpoena served upon any person under the provisions of this section, the MTB may request the Attorney General to seek the aid of the United States District Court for any District in which the person is found to compel that person, after notice, to appear and give testimony, or to appear and produce the subpoenaed documents before the MTB, or both.

5. New Subparts C and D are added immediately following Appendix B to Subpart B to read as follows:

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Subpart C—Preemption

§ 107.201 Purpose and scope.

(a) This subpart prescribes procedures by which (1) a State or a political subdivision of a State may determine whether a requirement of the Act or the regulations issued under the Act or regulations issued under the Act, and (2) a State or a political subdivision of a State may obtain a determination as to whether a requirement of that State or political subdivision, which is inconsistent with the Act or regulations issued under the Act, and therefore preempted by section 112(a) of the Act is not so preempted.

(b) For purposes of this subpart “political subdivision” includes a municipality; a public agency or other instrumentality of one or more State, municipal, or other political subdivisions of a State; or a public corporation, board, or commission established under the laws of one or more States.

(c) For purposes of this subpart regulations issued under the Act means the regulations contained in this subchapter, Subchapter C of this chapter, and 46 CFR Part 147.

§ 107.203 Application.

(a) Any State or political subdivision or any person affected by a requirement of a State or political subdivision may apply to the OHMO for an inconsistency ruling which includes an application for a determination that the requirement is not preempted will be treated and processed solely as an application for an inconsistency ruling.

Inconsistency Rulings

§ 107.205 Notice.

(a) If the applicant is other than a State or political subdivision, the applicant shall mail or deliver a copy of the application to the State or political subdivision concerned accompanied by a statement that the State or political subdivision may submit comments on the application to the OHMO within 45 days. The application filed with the OHMO must include a certification that the applicant has complied with this paragraph and must include the names and addresses of each State or political subdivision official to whom a copy of the application was sent.

(b) The OHMO may be serving notice on any other persons readily identifiable by the OHMO as persons who will be affected by the ruling sought or by publication in the Federal Register afford those persons an opportunity to file written comments on the application.

(c) Each person submitting written comments to the OHMO with respect to an application filed under this section shall send a copy of the comments to the applicant and certify to the OHMO that he has complied with this requirement. The OHMO may notify other persons participating in the proceeding of the comments and provide an opportunity for those other persons to respond.

§ 107.207 Processing.

(a) The Director, OHMO, may initiate an investigation of any statement in an application and shall invite all persons relevant to the application and any relevant facts obtained by that investigation. The Director, OHMO, may solicit and accept submissions from third persons relevant to an application and will provide the applicant an opportunity to respond to all third person submissions. In evaluating an application, the Director, OHMO, may consider any other source of information. The Director, OHMO, on his own initiative may convene a hearing or conference, if he considers that a hearing or conference will advance his evaluation of the application.

(b) The Director, OHMO, may dismiss the application without prejudice if:

(1) He determines that there is insufficient information upon which to base a ruling; or

(2) He requests additional information from the applicant and it is not submitted.

§ 107.209 Ruling.

(a) Upon consideration of the application and other relevant information received or obtained during the proceeding, the Director, OHMO, issue his ruling.

(b) Notwithstanding that application for a ruling has not been filed under § 107.203, the Director, OHMO, on his own initiative may issue a ruling as to whether a particular State or political subdivision requirement is inconsistent with the Act or the regulations issued under the Act is not preempted.

(c) In determining whether a State or political subdivision requirement is inconsistent with the Act or the regulations issued under the Act, the Director, OHMO, considers:

(1) Whether compliance with both the State or political subdivision requirement and the Act or the regulations issued under the Act is feasible; and

(2) The extent to which a State or political subdivision requirement is an obstacle to the accomplishment and execution of the purposes of the Act and the regulations issued under the Act.

(d) The ruling includes a written statement setting forth the relevant facts and the legal basis for the ruling and provides that anyone aggrieved thereby may file an appeal with the Director, MTB.

(e) The OHMO serves a copy of the ruling upon the applicant, any other person who participated in the proceeding and upon any other person readily identifiable by the OHMO as one who is affected by the ruling. A copy of each ruling is placed on file in the public docket. The OHMO may publish the ruling or notice of the ruling in the Federal Register.

(f) A ruling issued under this section constitutes an administrative determination as to whether a particular requirement of a State or local subdivision is inconsistent with the Act or the regulations issued under the Act. The fact that a ruling has not been issued under this section with respect to a particular requirement of a State or political subdivision carries no implication as to the consistency or inconsistency of that requirement with the Act or any regulations issued under the Act.

§ 107.211 Appeal.

Any person aggrieved by a ruling issued under § 107.205 may file an appeal with the Director, MTB. The appeal must be filed within 30 days of service of the ruling. There has not been an exhaustion of administrative remedies unless an appeal has been filed and the appellate process is completed by the issuance of an order by the Director, MTB, granting or denying the appeal.

Non-Preemption Determinations

§ 107.215 Application.

(a) Any State or political subdivision may apply to the OHMO for a determination that a particular existing requirement of that State or political subdivision which is inconsistent with the Act or the regulations issued under the Act is not preempted.

(b) Each application filed under this section for a nonpreemption determination must:


(2) Set forth the text of the State or political subdivision requirement for which the determination is being sought;

(3) Specify each requirement of the Act or the regulations issued under the Act with which the applicant seeks the State or political subdivision requirement to be compared for consistency; and

(4) State why the applicant believes the State or political subdivision requirement to be consistent or inconsistent with the requirements of the Act or the regulations issued under the Act.

(c) The filing of an application for a ruling under this section does not constitute grounds for noncompliance with any requirement of the Act or a regulation issued under the Act.
§ 107.217 Notice.

(a) The applicant State or political subdivision shall mail a copy of the application and any additional documents or other documents relating to the application to each person who is reasonably ascertainable by the applicant as a person who will be affected by the determination sought and the OHMO as persons who will be affected by the determination sought is inconsistent with the requirements of the Act or the regulations issued under the Act.

(b) Notwithstanding the provisions of paragraph (a) of this section, if the State or political subdivision determines that compliance with paragraph (a) of this section would be impracticable, the applicant shall:

(1) Comply with the requirements of paragraph (a) of this section with regard to those persons to whom it is reasonable and practicable to notify; and

(2) Include with the application filed with the OHMO a description of the persons or classes of persons to whom notice was not sent.

(c) The OHMO may require the State or political subdivision to provide notice in addition to that required by paragraphs (a) and (b) of this section, or may determine that the notice required by paragraph (a) of this section is not practicable, or that notice should be published in the Federal Register.

(d) The OHMO may serve notice on any other persons readily identifiable by the OHMO as persons who will be affected by the determination sought and may afford those persons an opportunity to file written comments on the application.

(e) Any person submitting written comments to the OHMO with respect to an application filed under this section shall send a copy of the comments to the applicant. The person shall certify to the OHMO that he has complied with the requirements of this paragraph. The OHMO may notify other persons participating in the proceedings and provide an opportunity for those other persons to respond.

§ 107.219 Processing.

(a) The Director, OHMO, may initiate an investigation of any statement in an application and utilize in his evaluation the results obtained by that investigation. The Director, OHMO, may solicit and accept submissions from third persons relevant to an application and will provide the applicant an opportunity to respond to all third person submissions. In evaluating an application, the Director, OHMO, on his own initiative may convene a hearing or conference, if he considers that a hearing or conference will advance his evaluation of the application.

(b) The Director, OHMO, may dismiss the application without prejudice if:

(1) He determines that there is insufficient information upon which to base a determination;

(2) Upon his request, additional information has not been submitted by the applicant; or

(3) The applicant fails to provide the comments to the OHMO.

(c) The State or political subdivision requirement does not unreasonably burden commerce; and

(d) The Director, OHMO, may dismiss the application without prejudice if:

(1) The applicant State or political subdivision expressly acknowledges in its application that the State or political subdivision requirement competes or conflicts with those of other States and political subdivisions.

(2) The Director, OHMO, may dismiss the application without prejudice if:

(2) Upon his request, additional information has not been submitted by the applicant; or

(3) The applicant fails to provide the comments to the OHMO.

§ 107.221 Determination and order.

(a) Upon consideration of the application and other relevant information received or obtained during the proceeding, the Director, OHMO, issues an order setting forth his determination.

(b) The Director, OHMO, may issue a non-preemption order only if he finds that the State or political subdivision requirement affords to the public a level of safety at least equal to that afforded by the requirements of the Act and the regulations issued under the Act and does not unreasonably burden commerce. In determining whether the State or political subdivision requirement unreasonably burden commerce, the Director, OHMO, considers the following factors:

(1) The extent to which increased costs and impairment of efficiency result from the State or political subdivision requirement.

(2) Whether the State or political subdivision requirement has a rational basis.

(3) Whether the State or political subdivision requirement achieves its stated purpose.

(4) Whether there is need for uniformity with regard to the subject concerned and if so, whether the State or political subdivision requirement competes or conflicts with those of other States and political subdivisions.

§ 107.225 Appeal.

Any person aggrieved by an order issued under § 107.221 may file an appeal with the Director, MTB. The appeal must be filed within 60 days of service of the notice required by § 107.219(d), the applicant may appeal the application as having been denied in all respects and may appeal therefrom as provided in § 107.225.

§ 107.225 Appeal.

Any person aggrieved by an order issued under § 107.221 may file an appeal with the Director, MTB. The appeal must be filed within 60 days of service of the notice required by § 107.219(d), the applicant may appeal the application as having been denied in all respects and may appeal therefrom as provided in § 107.225.

§ 107.250 Responsibility for enforcement.

In accordance with delegations of authority from the Secretary of Transportation set forth in Part 1 of this title, responsibility for enforcement of this subchapter and Subchapter C of this chapter is exercised by:

(a) The Federal Aviation Administration with respect to the transportation or shipment of hazardous materials by aircraft;
(b) The United States Coast Guard with respect to the transportation or shipment of hazardous materials by vessels; and
(c) The Federal Highway Administration with respect to the transportation or shipment of hazardous materials by highway vehicles;
(d) The Federal Railroad Administration with respect to the transportation or shipment of hazardous materials by railroad; and
(e) The DOT in all other respects. The MTBE exercises this enforcement responsibility through the OHMO.

§ 107.303 Purpose and scope.

This subpart describes the various enforcement authorities exercised by the OHMO and the associated sanctions and prescribes the procedures governing the exercise of those authorities and the imposing of those sanctions.

§ 107.305 Investigations.

(a) General. The OHMO may initiate investigations relating to compliance by any person with any provision of this subchapter for Subchapter C of this chapter or any order issued thereunder, or any court decree relating thereto. The OHMO encourages voluntary cooperation with its investigations. When circumstances warrant, however, subpoenas may be issued to compel the attendance of witnesses or the production of documents in accordance with and subject to § 5 U.S.C. 552.

(b) Investigators. Investigations are conducted by officials of the OHMO who are duly designated for that purpose. Each official so designated may administer oaths and receive affirmations in any matter under investigation by the OHMO.

(c) Notification. Any person who is under investigation by the OHMO and who is requested to furnish information or documentary evidence is notified as to the general purpose for which the information or evidence is sought.

(d) Termination. When the facts disclosed by an investigation indicate that further action is unnecessary or unwarranted at that time, the investigative file is closed without prejudice to further investigation by the OHMO at any time that circumstances so warrant.

(e) Confidentiality. Information received in an investigation under this section, including the identity of the person investigated and any other person who provides information during the investigation, shall, unless otherwise determined by the OHMO, remain confidential under the investigatory file except to the public disclosure requirements of 5 U.S.C. 552.

COMPLIANCE ORDERS

§ 107.307 Compliance orders generally.

When the OHMO has reason to believe that a person is engaging in conduct which involves a violation of any provision of this subchapter or Subchapter C of this chapter for which the OHMO can conduct proceedings pursuant to section 109(a) of the Act to determine the nature and extent of the violation and may thereafter issue an order directing compliance.

§ 107.309 Notice of probable violation.

(a) The OHMO begins a compliance order proceeding by serving a notice of probable violation charging him with violating one or more provisions of this subchapter.

(b) A notice of probable violation issued under this section includes:

(1) A statement of the provision[s] of this subchapter or Subchapter C of this chapter which the respondent is believed to be violating;

(2) A statement of the factual allegations upon which remedial action is being sought; and

(3) A statement of the remedial action being sought in the form of a proposed compliance order.

(c) The OHMO may amend a notice of probable violation issued under this section at any time before the entry of a final compliance order. If an amendment includes any new material allegations of fact or seeks new or additional remedial action, the respondent is given an opportunity to respond.

§ 107.311 Reply.

(a) Within 30 days of the service of a notice of probable violation issued under § 107.309, the respondent may file a reply with the OHMO, official who issued the notice of probable violation. That official may extend the 30-day period for good cause shown.

(b) The reply must be in writing, signed by the person filing it, and state with respect to each factual allegation whether it is admitted or denied. Even though formally denied, a factual allegation set forth in a notice of probable violation is considered to be admitted for purposes of the proceeding unless:

(1) Opposite the written statement of an individual having personal knowledge of the subject matter;

(2) Challenged as defective on its face together with a supporting explanation as to why it is believed to be defective; or

(3) Otherwise actively put at issue through the submission of relevant evidence.

(c) The reply must set forth any affirmative defenses and include a statement of the form and nature of proof by which those defenses are to be established.

(d) If it is necessary to respond to an amendment to the notice of probable violation, the respondent may amend his reply at any time before the issuance of an order under § 107.317.

(e) If the respondent elects not to contest one or more factual allegations, he should so state in the reply. An election not to contest a factual allegation is an admission of that allegation solely for the purpose of seeking a compliance order and constitutes a waiver of hearing as to that allegation but does not, by itself, constitute a waiver of the right to be heard on other issues. In connection with a statement of election not to contest a factual allegation, the respondent may propose an appropriate order for issuance by the Director, OHMO, or propose the termination of a contested order.

§ 107.313 Consent order.

(a) At any time before the issuance of an order under § 107.317, the OHMO and the respondent may execute an agreement for disposing of the case by the entry of a consent order. If the Director, OHMO, accepts the agreement, he issues an order in accordance with its terms. If the Director, OHMO, rejects the agreement, he directs that the proceeding continue.

(b) An agreement submitted to the Director, OHMO, under this section must include:

(1) A proposed compliance order suitable for the Director's signature;

(2) An admission of all jurisdictional facts;

(3) An express waiver of further procedural steps and of all right to seek judicial review or otherwise challenge or contest the validity of the order; and

(4) An acknowledgement that the notice of probable violation may be used to construe the terms of the order.

§ 107.315 Hearing.

(a) When a respondent files a reply contesting the allegations in a notice of proposed violation issued under § 107.309 or when the OHMO and the respondent fail to agree upon an acceptable consent order, the Director, OHMO, or an official designated by him, convenes and presides over a hearing on the proposed compliance order.

(b) The presiding official may:

(1) Administer oaths and affirmations;

(2) Issue subpoenas as provided by § 107.13;

(3) Adopt procedures for the submission of evidence;

(4) Take cause depositions to be taken;

(5) Rule on offers of proof and receive relevant evidence;

(6) Examine witnesses at the hearing;

(7) Convene, recess, reconvene, adjourn and otherwise regulate the course of the hearing;

(8) Hold conferences for settlement, simplification of the issues or any other proper purpose; and

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§ 107.317 Presiding officer's decision.

(a) After consideration of evidence, the presiding officer may dismiss the notice of proposed violation or issue an order directing compliance. The order will include a statement of finding and conclusions as well as the reasons therefore on all material issues of fact, law, and discretion.

(b) A compliance order issued under this section is effective upon service on the respondent unless otherwise provided therein.

§ 107.319 Compliance order for immediate compliance.

(a) Notwithstanding §§ 107.309 through 107.315, the Director, OHMIO, may issue a compliance order for immediate compliance, which is effective upon issuance, and until rescinded or suspended, if he finds:

(1) There is strong probability that a violation is occurring or is about to occur; or

(2) The violation poses an unreasonable risk to health or to safety of life or property; and

(3) The public interest requires the avoidance or amelioration of that unreasonable risk through immediate compliance and waiver of the procedures afforded under §§ 107.309 through 107.315. The order may issue a compliance order for immediate compliance if it appears that the criteria set forth in paragraph (a) of this section are satisfied. The Director, OHMIO, may issue a compliance order for immediate compliance even if the 30-day period for reply specified in § 107.311(a) has not expired.

(c) At any time after a compliance order has become effective, the Director, MTB, or his delegate may request the Attorney General to bring an action for appropriate relief in accordance with § 107.331.

§ 107.321 Appeal.

(a) A person aggrieved by a compliance order or a compliance order for immediate compliance may file an appeal with the Director, MTB. The appeal must be filed within 20 days after service of the compliance order.

(b) The filing of an appeal does not stay the effectiveness of the order unless the Director, MTB, expressly so provides.

INJUNCTIVE ACTION

§ 107.331 Injunctions generally.

Whenever it appears to the OHMIO that a person has engaged, is engaged, or about to engage in any act or practice constituting a violation of any provision of this subchapter or Subchapter C of this chapter which the respondent is believed to have violated, the Director may issue a compliance order proceeding or other administrative hearing or formal proceeding to abate the risk of that harm. The Director, MTB, or his delegate, may bring an action in the appropriate United States District Court for such relief as is necessary or appropriate, including mandatory or prohibitive injunctive relief, interlocutory relief, and punitive damages as provided by section 111(a) of the Act.

§ 107.333 Injunctive relief.

Whenever it appears to the OHMIO that there is a substantial likelihood that death, serious illness, or severe personal injury will result from the transportation of a particular hazardous material before a compliance order proceeding or other administrative hearing or formal proceeding to abate the risk of that harm can be completed, the Director, MTB, or his delegate, may bring an action in the appropriate United States District Court for an order suspending or restricting the transportation of that hazardous material or for such other equitable relief as is necessary or appropriate to ameliorate the hazard as provided by section 111(b) of the Act.

CIVIL PENALTIES

§ 107.341 Civil penalties generally.

When the OHMIO has reason to believe that a person has knowingly committed an act which is a violation of any provision of this subchapter or Subchapter C of this chapter which the OHMIO exercises enforcement responsibility or of any exemption issued under Subpart B of this part, it may conduct proceedings to assess and, if appropriate, compromise a civil penalty.

§ 107.343 Maximum penalties.

(a) A person who knowingly violates a requirement of this subchapter applicable to the importing of hazardous materials or to the causing of them to be transported, or shipped, or which are liable to the transportation of hazardous materials in commerce, to any civil penalty of not more than $10,000 for each violation. When the violation is a continuing one, each day of the violation constitutes a separate offense.

(b) A person who knowingly violates a requirement of this subchapter applicable to the manufacture, fabrication, marking, maintenance, reconditioning, repair, or testing of a package or container which is represented, marked, certified or sold by that person for use in the transportation of hazardous materials in commerce is liable for a civil penalty of not more than $10,000.

§ 107.345 Notice of probable violation.

(a) The OHMIO begins a civil penalty proceeding by serving a notice of probable violation on a person charging him with having violated one or more provisions of this subchapter or Subchapter C of this chapter.

(b) A notice of probable violation issued under this section includes:

(1) A statement of the provision(s) of this subchapter or Subchapter C of this chapter which the respondent is believed to have violated;

(2) A statement of the factual allegations upon which the proposed civil penalty is being sought;

(3) Notice of the maximum amount of civil penalty for which the respondent may be liable;

(4) Notice of the amount of the preliminary assessed civil penalty;

(5) A description of the manner in which the respondent should make payment of any money to the United States;

(6) A statement of the respondent's right to present written or oral explanations, information or any materials in answer to the allegations or in mitigation of the penalty; and

(7) A statement of the respondent's right to request a hearing and the procedures for requesting a hearing.

§ 107.347 Reply.

(a) Within 30 days of the service of a notice of probable violation issued under § 107.345, the respondent may:

(1) Pay the preliminary assessment as provided in § 107.349(a) and thereby close the case;

(2) Make an informal response as provided in § 107.351; or

(3) Request a hearing as provided in § 107.353.

(b) The OHMIO official who issued the notice of probable violation may extend the 30-day period for good cause shown.

(c) Failure of the respondent to reply by taking one of the three actions described in paragraph (a) of this section within the period provided constitutes a waiver by the respondent of his right to appeal and contest the allegations presented to and by the OHMIO, without further notice to the respondent, to find the facts to be as alleged in the notice of probable violation and order the assessment of an appropriate civil penalty.


§ 107.349 Payment of penalty.

(a) Payment of a civil penalty should be made by certified check or money order payable to the Treasurer of the United States and sent to the Assistant General Counsel for Materials Transportation Law, Department of Transportation, Washington, D.C. 20590. Before an order assessing a civil penalty is referred to the Attorney General for collection, the respondent may offer to compromise for a specific amount bySubmitting a certified check or money order for that amount to the Assistant General Counsel who may accept or reject it. If it is accepted, the respondent is notified in writing that the acceptance is in full settlement of the civil penalty for the violation.

§ 107.351 Informal response and assessment.

(a) If a respondent elects to make an informal response to a notice of probable violation, he shall submit to the OHMO official who issued the notice such written explanations, information or other materials as he may desire in answer to the charges or in mitigation of the proposed penalty.

(b) The respondent may include in his informal written response a request for a conference. Upon receipt of such a request, the OHMO arranges for a conference as soon as practicable at a time and place of mutual convenience.

(c) Written explanations, information or material submitted by the respondent and relevant information presented during any conference held under this section are considered by the OHMO in reviewing the notice of proposed violation and determining the fact of violation and the amount of any penalty to be assessed.

(d) After consideration of an informal response including any relevant information presented at a conference, the Director, OHMO, may dismiss the notice of probable violation in whole or in part. If he does not dismiss it in whole he may issue an order assessing a civil penalty.

§ 107.355 Request for hearing.

(a) If a respondent elects to request a hearing, he shall submit a written request to the Director, OHMO. The request must:

(1) State the name and address of the respondent and of the person signing the request if different from the respondent;

(2) State with respect to each allegation whether it is admitted or denied;

(3) State with particularity the issues to be raised by the respondent at the hearing.

(b) After a request for hearing which complies with the requirements of paragraph (a) of this section, the Director, OHMO, schedules a hearing for the earliest practicable date.

(c) The Director, OHMO, may grant extensions of time of the commencement of the hearing for good cause shown.

§ 107.355 Hearing.

(a) When a hearing is requested and scheduled under § 107.353, the Director, OHMO, or his designee by him, convenes and presides over the hearing. To the extent practicable, the hearing will be held in the general vicinity of the place where the alleged violation occurred or a place convenient to the respondent. Testimony by witnesses shall be given under oath and the hearing shall be recorded verbatim.

(b) The presiding official may:

(1) Administer oaths and affirmations;

(2) Issue subpoenas as provided by § 107.13;

(3) Adopt procedures for the submission of evidence in written form;

(4) Take or cause depositions to be taken;

(5) Rule on offers of proof and receive relevant evidence;

(6) Examine witnesses at the hearing;

(7) Convene, recess, reconvene, adjourn and otherwise regulate the course of the hearing;

(8) Hold conferences for settlement, simplification of the issues or any other proper purpose; and

(9) Take any other action authorized by or consistent with the provisions of this subpart pertaining to civil penalties.

§ 107.357 Presiding officer's decision.

(a) After consideration of the evidence of record, the presiding officer may dismiss the notice of probable violation in whole or in part. If he does not dismiss it in whole he will issue and serve on the respondent an order assessing a civil penalty. The order will include a statement of findings and conclusions as well as the reasons therefor on all material issues of fact, law, and discretion.

(b) If, within 20 days after service of an order assessing a civil penalty, the respondent does not pay the civil penalty or file an appeal as provided in § 107.359, the order becomes final.

§ 107.359 Assessment considerations.

In assessing a civil penalty under §§ 107.351 and 107.355, the assessment is made only after considering:

(1) The nature and circumstances of the violation;

(2) The extent and gravity of the violation;

(3) The degree of the respondent's culpability;

(4) The respondent's history of prior offenses;

(5) The respondent's ability to pay;

(6) The effect on the respondent's ability to continue in business; and

(7) Such other matters as justice may require.

§ 107.361 Appeal.

(a) A respondent aggrieved by a presiding officer's decision and order issued under § 107.357 assessing civil penalties may file an appeal with the Director, MTB. The appeal must be filed within 20 days of the presiding officer's order.

(b) If the Director, MTB, affirms the assessment and the respondent does not pay the civil penalty within 20 days after service of the Director's decision on appeal, the case may be referred to the Attorney General with a request that an action to collect the penalty be brought in the appropriate United States District Court.

§ 107.371 Criminal penalties generally.

Section 110(b) of the Act (49 U.S.C. 1886(b)) provides a criminal penalty of a fine of not more than $25,000 and imprisonment for not more than five years, or both, for any person who willfully violates a provision of the Act or a regulation issued under the Act.

§ 107.373 Referral for prosecution.

If an inspector or other employee of the OHMO becomes aware of a possible willful violation of the Act, this subchapter or Subchapter C of this chapter for which the OHMO exercises enforcement responsibility, he reports to the Office of the Assistant General Counsel for Materials Transportation Law. If appropriate, the Assistant General Counsel refers the report to the Department of Justice for criminal prosecution of the offender.

Effective date: This amendment is effective January 3, 1977.

(49 U.S.C. 1653-1811 and 49 CFR 197.9(e).)

Issued in Washington, D.C., on August 31, 1976.

JAMES T. CRISS, Jr.
Director,
Materials Transportation Bureau.

[FR Doc. 70-2536 Filed 9-7-76; 8:45 am]


HAZARDOUS MATERIALS REGULATIONS

Reissuance

On March 3, 1976, the Materials Transportation Bureau (MTB) pub-
lished a notice of proposed rulemaking in the Federal Register identified as Docket No. HM-134; Notice No. 76-2. In that notice, the MTB proposed to amend certain of the hazardous materials regulations for which it has responsibility to expressly reflect a reissuance of those regulations under the authority of the Hazardous Materials Transportation Act (Title I of Pub. L. 93-633) (HMTA). To accomplish that purpose the MTB proposed to revise the authority citations and, where necessary, the applicability of the hazardous materials regulations in 49 CFR Parts 103, 46 CFR Parts 64 and 146, and 49 CFR Parts 170-179.

The basis for the March 3 proposal is found in §114(b) (2) of the HMTA:...

The Secretary shall take all steps necessary to bring orders, determinations, rules, and regulations into conformity with the purposes and provisions of this title as soon as practicable...

This reissuance, one step in meeting the mandate of section 114(b) (2), provides the necessary legal connection being made between the hazardous materials regulations and the authorities vested in the Secretary of Transportation by the HMTA so that the provisions of the regulations remain the same as immediately prior to the reissuance.

Although the MTB considered the proposed reissuance to be mandatory and therefore leaving the Bureau without discretion in the matter, interested persons were invited to participate in the HM-134 rulemaking by submitting comments with respect to matters which they regarded as being outside the proposed reissuance. All comments received on Docket HM-134 have been given full consideration by the Bureau before a decision was made on the amendments. Of the many comments received, a number have been determined to be outside the scope of the HM-134 proposal. Such comments have been or will be given separate consideration and may be the subject of future rulemaking action. The remaining comments, including those offering full support for the proposed reissuance, concerned themselves with the following:

- Lack of adequate notice in HM-134 as to specific substantive changes to existing regulations.
- Retaining certain existing citations of authority to the regulations.
- Deferring the proposed reissuance until the amendments under Dockets HM-112 and HM-103 are finalized.
- Deferring the proposed reissuance pending recodification and simplification of the regulations.
- DOT jurisdiction over non-commercial as well as commercial transportation.
- Preemption of State and local laws and regulations.

An allegation that the reissuance of 49 CFR 173.115(a) under the terms of the proposal would be in violation of Sections 104 and 105(a) of the HMTA.

The need to clarify the applicability of the Shipping Container Specifications of Part 178 of 49 CFR before reissuing those specifications.

The issues raised by these comments will be addressed separately in the discussion that follows.

Several comments expressed the attitude that the proposed reissuance was merely a technical or housekeeping amendment and that HM-134 could not accomplish the purpose of making any substantive changes in the nature, extent, and effect of the hazardous materials regulations.

The Materials Transportation Bureau does not consider the amendments to be merely technical or housekeeping in nature. The Congressional mandate of section 114(b) (2), to which the proposal was in response, envisages much more than that. As previously stated, the reissuance will result in the necessary legal connection being made between the hazardous materials regulations and the authorities vested in the Secretary of Transportation by the HMTA and the authorities vested in the Secretary of Transportation by the HMTA so that the provisions of the regulations be made consistent with the statutory mandate of section 114(b) (2) of the HMTA. This amendment will do no more than was proposed in the March 3rd notice.

Retention of Existing Authority
Citations

Because the Transportation of Explosives Act (18 U.S.C. 834-835) has not been repealed, one comment urged that the existing authority citations to that Act in 49 CFR Parts 171-179 be retained. The Bureau believes that to do so would not be consistent with the statutory mandate of section 114(b) (2) of the HMTA which requires the hazardous materials regulations to be brought into "conformity with the purposes and provisions of the HMTA as soon as practicable."

Relationship to HM-112 & HM-103

Subsequent to the March 3rd notice, the amendments under Dockets HM-112 and HM-103 were published (41 FR 15972, April 15, 1976). Those amendments became effective July 1, 1976, and resulted in a conclusion that the hazardous materials regulations for all modes in 49 CFR. The consolidation revised and relocated to 49 CFR certain hazardous materials regulations previously in 14 and 46 CFR. The action resulted in the revocation of 14 CFR Part 103 and a substantial reduction of 46 CFR Part 148 (41 FR 15972, 41 FR 26110). Therefore, amendments to authority citations in 41 CFR Part 103 proposed by this rulemaking are unnecessary and amendments to authority citations in 46 CFR Part 148 need not be as extensive as originally anticipated.

The comments requesting the Bureau to defer action on the proposed reissuance until final action on outstanding hazardous material Dockets HM-103 and HM-112 have been overtaken by events. Since that time those dockets have been finalized and became effective July 1, 1976 (41 FR 15972). The fact that mandatory compliance with various amendments under Dockets HM-103 and HM-112 is not required until after July 1, 1976, is not considered by
the Bureau to a valid reason for further delay in finalizing HM-112. The regulations as amended by HM-103 and HM-112 would be consistent with the applicable legal standards. A violation of any of those standards subjects the violator to the applicable penalty provided by statute unless it is specifically stipulated that the violation is an action authorized by the effective date provision under Dockets HM-103 and HM-112, as amended at 49 FR 36014, to be performed in the manner provided by the regulations in existence on June 30, 1976, and (2) that action does in fact comply with the regulations as they existed on June 30, 1976.

Reconciliation

One comment, urged the Bureau to consider completely recodifying the existing hazardous material regulations prior to their reissue under the HMATA. In light of the Congressional mandate embodied in 114(b) (2) of the HMATA and a recodification that may take a year or more to complete, the Bureau must reject this suggested approach.

By finalizing the proceedings in Dockets HM-103 and HM-112 the Materials Transportation Bureau completed the first major phase of its continuing effort to improve, update, and simplify the regulations governing the shipment and transportation of hazardous materials. The next phase will be a recodification of those hazardous materials regulations over which the Bureau has authority. Where the principal purpose of HM-103 and HM-112 was the consolidation and substantive improvement of specific segments of the regulations, the purpose of the recodification phase will be to rearrange and revise the language of the regulations in a more comprehensible and accessible form to reduce inconsistency, redundancy and obsolescence. The changes made in 49 CFR Parts 171, 172, 174, 175 and 176 by Dockets HM-103 and HM-112 have already instituted many of the changes that would be ordinarily achieved by a pure codification. Therefore, future codification efforts will be unnecessary for 49 CFR Parts 171, 172, 175 and 176.

If it were prepared to initiate formal codification rulemaking focusing on Parts 173 and 179, the Bureau is of the opinion that a reasonable period should be allowed for the major changes affected by HM-103 and HM-112 to season and for persons affected by those changes to become accommodated to them.

NONCOMMERCIAL TRANSPORTATION

One comment reads as follows:

The statute [HMATA] does not limit the DOT’s jurisdiction to commercial transportation. Historical experience in administering the hazardous materials regulations, however, supports the conclusion that regulations for public safety do not require regulations governing personal transportation in personal vehicles. It is recommended that this conclusion be reflected in regulations adopted under HM-103, thereby continuing the traditional limitation of coverage to commercial transportation.

While, as pointed out earlier, the action being taken by the Bureau in this proceeding does not expand the coverage of the hazardous materials regulations to any class of ships or transporters who are not already subject to those regulations, it should be recognized that the express policy of Congress in enacting the HMATA is to give the Secretary of Transportation broad authority to promulgate necessary regulations. The Secretary shall have the authority to establish the regulations and enforce the provisions of this section. Congress, in enacting the HMATA, did not exempt hazardous materials regulations from the FRA’s jurisdiction to commercial transportation. As broaden its jurisdiction to commercial transportation, the Bureau believes it is appropriate to propose the recodification phase that may take a year or more to complete.

The remaining comments with regard to preemption ran the spectrum of full support for the reasonable and its effect on the preemption provision of the HMATA; to suggesting that until efficient procedures for making preemption determinations have been established, preemption provisions in existence on the effective date of the HMATA be presumed to not preempt unless the Bureau makes a determination to the contrary; to urging the DOT to reissue any regulations which would result in the presumption of any inconsistent State and local regulations and law. These last two comments reveal a basic misunderstanding of the relationship between the power of Congress in enacting the HMATA and the preemption provisions of the HMATA. The Bureau believes a discussion to clarify this misunderstanding is in order.

The relationship between the authority of the Federal Government and that of State and local governments, with respect to the safe transportation of hazardous materials, was specifically addressed by Congress in section 112 of the HMATA.

In Senate Report No. 93-192 accompanying S. 4067, which was eventually enacted as the HMATA, the Committee on Commerce in discussing section 112 stated:

The Committee endorses the principle of Federal preemption in order to preclude a duplication of effort and the potential for varying as well as conflicting regulations in the area of hazardous materials transportation.

The express provision of preemption in section 112 of the HMATA provides that: "Except as provided in subsection (b) of this section, any requirement of a State ... which is inconsistent with any regulation issued under the HMATA is preempted." Section 112(a)

Section 112(b) provides that a State regulation not consistent with any requirement set forth in a regulation issued under the HMATA is not preempted if upon the application of an appropriate State agency, the Secretary determines, in accordance with procedures prescribed by the regulations, that such requirement (1) affords an equal or greater level of protection to the public than is afforded by the regulations of the HMATA set forth in the regulation issued under the HMATA, and (2) does not unreasonably burden commerce. The comment-
upon a finding by the Secretary, in his discretion, that the transportation of a particular quantity and form of material in commerce may pose an unreasonable risk to health and safety or property, he shall designate such quantity and form of material as a hazardous material (emphasis supplied).

The Bureau takes this opportunity to point out that section 104 permits the Secretary to designate a material as hazardous if it may be reasonably inferred that the material is capable of posing such a risk. The fact that the provisions of this section with respect to the flammable liquid definition have been discussed at length in Docket HM-102 and are summarized in the discussion which follows. Although nearly all of the significant activity in Docket HM-102 preceded the HMTA, the procedures used to reach the conclusions of that rulemaking are in full accord with the new requirements of section 104.

These same commentors also assert that the reissuance of §173.115(a) violates section 105(a) of the HMTA, i.e., that the Bureau did not provide "an opportunity for informal, oral presentation" on the proposal. It was under Dockets HM-2 and HM-5 that the Hazardous Materials Regulations Board (predecessor of the MTB) published the currently applicable definition of flammable liquids found in 49 CFR 173.115 (4 CFR 22263, May 22, 1975). A historic review of the efforts that lead to that publication will also lead to a better understanding of the Bureau's reaction to this assertion with regard to section 105(a) of the HMTA.

The first notice of proposed rulemaking relative to Docket HM-102 appeared in the Federal Register on February 27, 1968 under Docket HM-3 (39 FR 32862). Subsequent to that notice meetings were held with industry and trade associations such as Manufacturing Chemists Association, National Paints and Coatings Association, the National Faints and Coatings Association, the American Petroleum Institute, the Society of the Plastics Industry, Inc., and the American Society for Testing and Materials. Of concern was the appropriate definition for flammable liquids considering the transportation environment, and the need for compatibility with the flammable liquid definitions of other government agencies.

The recommended test method specified for evaluating the flammability hazard of liquids was discussed extensively with these groups.

In 1969, a contract (DOT-OS-00007) was established with the Bureau of Mines for an evaluation of the Department's hazardous materials classification system and test methods. This resulted in the publication of a report in April 1970 titled, "Recommendation of Flash Point Method for Evaluation of Flammability Hazard of Materials Transported in Flammable Liquids." The report contained an analysis of the flammability hazard presented in transportation; and recommended a definition for flammable liquids, and a method of test as a criterion for this definition. An additional contract (DOT-OS-00038) was let in 1969 for the study of hazardous materials regulations under the authority of the HMTA. An extensive report was published under this contract in October 1971 by the American Automobile Transportation Corporation标题："A Survey of Hazardous Material Regulations." Much of this study was devoted to the temperature environment to be encountered in transportation. Based on these two studies, the proposed definition of a flammable liquid was considered to be somewhat conservative with respect to the maximum temperature limit to be encountered in transportation.

Representatives of the Consumer Product Safety Commission, and the Department of Labor's Occupational Safety and Health Administration (OSHA) were specifically asked to participate in the discussions and evaluation of the classification problem. On May 29, 1971, OSHA published its Proposed Flammable and Combustible Liquids (29 CFR 1910.106 effective date August 31, 1971). They specify a definition for flammable liquids identical with the definition proposed by the MTB. A public hearing was held by OSHA concerning this standard at which time the desirability of uniformity of definition between the Department of Labor and Department of Transportation was discussed.

As a result of these many efforts, modifications of the proposed amendment were made at various times. The more important modifications included:

1. Deletion of the open cup as an alternate test method. [HM-07 (32 FR 18203), December 5, 1967]
2. Additional requirements for combustible liquids and the addition of certain exceptions for flammable liquids newly regulated under this amendment. [HM-102 (30 FR 2768), January 24, 1974]
3. Addition of a Gelboflux tester as an alternate test method and additional exceptions for certain specific commodities. [HM-103 (40 FR 22263), May 23, 1975]

Four additional notices appeared in the Federal Register during this time period. These were concerned primarily with an extension of the time period for consideration of this rulemaking. Extensive files on this subject are open to the public. The Bureau maintains a public reading room and welcomes visits by any interested party.

Regardless of the statutory authority for a particular proposed regulation, when the Bureau issues a notice of proposed rulemaking, it schedules a public hearing on its own motion if it believes that the rulemaking is likely to be materially advanced by supplementing the written comments with oral presentations. In the case of proposed hazardous materials regulations under section 105(a) of the Hazardous Materials Transportation Act, the Bureau is fully cognizant of the "opportunity for informal, oral presentation" provision which distinguishes that section. We do not, how-

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ever, subscribe to the view that "a hearing is now guaranteed by law." We perceive the true state of the law on this matter to be something less ambiguous. Even where a statute goes further than section 105(a) and states in unqualified terms that a hearing shall be held, a hearing is not required if the other reasons asserted for holding it are legally insufficient. Dyestuffs and Chemicals, Inc. v. Flemming, 271 F. 2d 281 (5th Cir. 1969), cert. denied, 362 U.S. 911 (1960). In accord is the § 102.27(a) provision of the Bureau's procedural regulations which provides that a petition for a hearing will be granted only if the petitioner shows good cause for the hearing.

While the Bureau routinely schedules one or more informal public hearings on all of its significant hazardous materials rule-making proposals, as it did in 29 CFR 102 which resulted in the change to the definition of "flammable liquid," there is no compelling legal or policy reason for the Bureau to hold hearings on those occasions when there is nothing material to be heard.

**Clarification of Ambiguities in Regulations Being Made Applicable to Manufacturers**

Several comments on the proposed reissue received from container manufacturers and associations representing these manufacturers are noted. As a result of market forces, reissuance of 49 CFR Part 178 should be deferred until certain clarifications are made to the provisions of that Part. Prior to the enactment of the HTMA, the DOT lacked any direct jurisdiction over manufacturers of packages and containers that are used for transporting hazardous materials in commerce. Therefore, detailed regulations spelling out the requirements for containers were necessarily addressed to a class of persons subject to DOT jurisdiction (i.e., shippers). Congress saw this as a serious weakness that frustrated the DOT's efforts to adequately regulate for the safe transportation of hazardous materials. Congress cured this weakness by vesting in the Secretary of Transportation, under various provisions of the HTMA, regulatory and enforcement authority over those manufacturers. One goal of this reissuance is to implement that new authority, therefore, necessitating certain changes to Parts 178 and 179 to delineate the new responsibilities of container manufacturers resulting from the reissuance of those parts under the HTMA.

To accomplish that purpose, Parts 178 and 179 have been amended to provide that any person performing a function prescribed by either part must perform that function in accordance with the applicable part. The Bureau is specifically requiring that the manufacturer mark the packaging or container with the DOT specification. That mark will be understood to designate the manufacturer, that the functions performed by the manufacturer, have been performed in compliance with the applicable part.

Because of the DOT's historical lack of direct jurisdiction over container manufacturers, Parts 178 and 179 presently prescribe many functions with regard to packagings and containers that are, by their nature, performed after the package or container has left the control of the manufacturer. The function of a packaging or container meets all the applicable specification requirements when ultimately used in the transport of hazardous materials. In other words that the manufacturer of a packaging or container inform each person to whom that packaging or container is transferred or any specification requirements which have not been met at the time of transfer. In addition, § 173.22(a) has been revised to clarify the shipper's responsibility for compliance with packaging and container specifications. The revised paragraph requires that when a shipper performs a function covered by, or having an effect on a specification requirement of Part 178 or 179, the shipper must perform that function in accordance with the specification. (This revision to § 173.22 was proposed under Docket No. 117 published on June 14, 1974 (39 FR 20865).)

As a result of market forces, i.e., shippers required by regulation to transport hazardous materials in containers; meeting the requirements of Parts 178 and 179, container manufacturers have produced their product in compliance with those specifications. One commenter stated, "we manufacture our [container] according to DOT specification * * * or exemption. All tests are also performed to the same specification."

Thus, while proclaiming past voluntary compliance with DOT container manufacture and testing specifications, these manufacturers are now heard to say that the same specifications are so vague and questionable that proposed reissuance would put a very unfair burden on them by imposing the risk of civil penalties and criminal prosecution. They assert that such burdens should not be placed on the manufacturer until the vagueness and ambiguity are removed from the specifications.

The Bureau is not persuaded by these comments to defer reissuance of 49 CFR Parts 178 and 179 under the authority of the HTMA. Several reasons lead to this conclusion:

Container manufacturers' own past practices under the "chipper" regulations with regard to manufacture and testing provide guidance as to the purpose and meaning of the regulations governing the design and construction of containers;

Container manufacturers' long exposure to the past practices of the DOT with regard to the interpretation and enforcement of manufacturing and testing specifications with respect to shippers also provide guidance as to future DOT practices with regard to manufacturers;

As in the case of any Federal compliance or enforcement action, any container manufacturer who may be accused of non-conformance to a regulation which he considers vague or ambiguous is entitled to assert that as a defense; and

Container manufacturers have the same rights and opportunities to request interpretations of and changes to the regulations as are currently exercised with great frequency by the shippers and carriers who have long been directly subject to the Federal hazardous materials transportation regulations.

In consideration of the foregoing 49 CFR Parts 171, 172, 173, 174, 176, 177, 178, and 179 are amended as follows:

1. In Part 171, the authority citation following the table of contents is revised to read as follows:

**PART 171—GENERAL INFORMATION, REGULATIONS, AND DEFINITIONS**

**Authority:** 49 U.S.C. 1804, 1803; 49 CFR 1.53(c), unless otherwise noted.

2. In § 171.2, a new paragraph (c) is added to read as follows:

§ 171.2 General transportation requirements.

(c) No person may represent, mark, certify, or sell a packaging or container as meeting the requirements of this subchapter governing the use of that packaging or container in the transportation in commerce of a hazardous material unless the packaging or container is manufactured, fabricated, marked, maintained, reconditioned, or repaired, as the case may be, in accordance with this subchapter.

3. In § 171.8, a definition for "United States" is added alphabetically to read as follows:

§ 171.8 Definitions and abbreviations.

United States means the fifty States, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, American Samoa, or Guam.

4. In Part 172, the authority citation following the table of contents is revised to read as follows:

**PART 172—HAZARDOUS MATERIALS TABLE AND HAZARDOUS MATERIALS COMMUNICATION REGULATIONS**

**Authority:** 49 U.S.C. 1803, 1804; 49 CFR 1.53(c), unless otherwise noted.

5. In § 172.3, a new paragraph (b) is added to read as follows:

§ 172.3 Applicability.

(b) When a person, other than one of those provided for in paragraph (a) of this section, performs a packaging labeling or marking function required by this part, that person shall perform the function in accordance with this part.
6. In Part 173, the authority citation following the table of contents is revised to read as follows:

PART 173—SHIPPERS—GENERAL REQUIREMENTS FOR SHIPMENTS AND PACKAGINGS

Authority: 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.63(e), unless otherwise noted.

7. In § 173.1, a new paragraph (c) is added to read as follows:

§ 173.1 Purpose and scope.

(c) When a person other than the person preparing a hazardous material for shipment performs a function required by this part, that person shall perform the function in accordance with this part.

8. In § 173.22, paragraph (a) is revised to read as follows:

§ 173.22 Shipper’s responsibility.

(a) When a container is supplied by the shipper, the shipper shall be responsible to determine that shipments of hazardous materials

9. In § 173.24, paragraph (c) is revised to read as follows:

§ 173.24 Standard requirements for all packages.

(c) Each specification container must be marked as follows:

(i) In an unobstructed area with letters and numerals identifying the container specification (e.g., DOT-1A, DOT-17E-304HT, DOT-23G40). See § 178.0-2 of this subchapter.

(ii) The name and address or symbol of the manufacturer of the container must be marked on the packaging to provide adequate accessibility, permanency, and contrast so as to be readily apparent and understood.

(iv) Unless otherwise specified, letters and numerals must be at least 1/2 inch high.

(v) Packaging which does not comply with the applicable specification listed in Parts 178 and 179 of this subchapter must not be marked to indicate such compliance (see § 178.0-2 and § 179.1 of this subchapter).

10. In Part 174, the authority citation following the table of contents is revised to read as follows:

PART 174—CARRIAGE BY RAIL

Authority: 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.63(e), unless otherwise noted.

11. In § 176, the authority citation following the table of contents is revised to read as follows:

PART 176—CARRIAGE BY VESSEL

Authority: 49 U.S.C. 1707(a) (a-c); 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.63(e), unless otherwise noted.

13. In § 177, the authority citation following the table of contents is revised to read as follows:

PART 177—CARRIAGE BY PUBLIC HIGHWAY

Authority: 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.63(e), unless otherwise noted.

15. In Part 178, new §§ 178.0, 178.0-1, and 178.0-2 are added immediately preceding Subpart A to read as follows:

§ 178.0 Purpose, scope, and applicability.

§ 178.0-1 Purpose, scope, and applicability.

This part prescribes the manufacturing and testing specifications for packaging and containers used for the transportation of hazardous materials in commerce.

§ 178.0-2 Applicability.

(a) Any person who performs a function prescribed in this part, shall perform that function in accordance with this part.

(b) When this part requires (either expressly or by reference to § 173.24 of this subchapter) a packaging or container to be marked with a DOT specification (for example, DOT-1A, DOT-17E-304HT, DOT-23G40), compliance with that requirement is the responsibility of the packaging or container manufacturer. Marking the packaging or container with the DOT specification shall be understood to certify compliance by the manufacturer, that the functions performed by the manufacturer, as prescribed in this part, have been performed in compliance with this part. (See also § 173.28 “Reuse of containers.” That section envisions the marking of containers to be performed by a person other than the original manufacturer.)

14. In §§ 178.1-8, 178.2-6, 178.3-6, 178.4-7, 178.5-7, 178.6-8, 178.7-7, 178.7-8, 178.7-9, 178.7-12, 178.13-5, 178.14-7, 178.162-4, 178.186-4, and 178.218-10, the second sentence in paragraph (a) (1) is deleted; and paragraph (a) (2) is read as follows:

(a) (2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

17. In § 178.15-7, paragraph (b) is revised to read as follows:

§ 178.15-7 Marking.

(b) Each container must also be marked with the name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

18. Section 178.18 is revised to read as follows:

§ 178.18—Marking on each container.

(a) Marking on top head plainly and permanently as follows:

(1) DOT-43A.

(2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above, below, or following that mark. Symbol, if used, must be registered with the Bureau of Explosives.

(2) Rated gallonage and year of manufacture (for example, 5-50).

19. § 178.19-6 is revised to read as follows:

§ 178.19-6 Marking.

(a) Each container must be permanently marked by embossment in letters and figures at least 1/2 inch in size as follows:

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§ 178.20-1 Capacity, thickness of metal, test and closure.

(a) Containers of 5 to 13 gallons capacity are covered by this specification. Actual capacity of the container must be the marked capacity plus 5 percent minimum.

(b) Each container must be permanently marked with figures and letters at least \( \frac{3}{4} \) inch high to show:

1. DOT-3T.
2. Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.
3. Month and year of manufacture.
4. (Rated) capacity.

§ 178.33-9 Marking.

(a) By means of printing, lithographing, embossing, or stamping, each container must be marked to show:

1. DOT-2L.
2. Name or symbol of person making the mark specified in paragraph (a) (2) of this section. Symbol, if used, must be registered with the Bureau of Explosives.
3. Month and year of manufacture.
4. (Rated) capacity.

(b) Marking: Each container must be permanently marked with figures and letters at least \( \frac{3}{4} \) inch in size to show:

1. DOT-2L.
2. Name or symbol of person making the mark specified in paragraph (a) (2) of this section. Symbol, if used, must be registered with the Bureau of Explosives.
3. Month and year of manufacture.
4. (Rated) capacity.

§ 178.35-3 Construction, capacity and marking.

(a) Each container must be permanently marked by embossment in figures and letters at least \( \frac{3}{4} \) inch in size to show:

1. DOT-3U.
2. Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.
3. Month and year of manufacture.
4. (Rated) capacity.

§ 178.24-5 Marking.

(a) Each container must be permanently marked by embossment in figures and letters at least \( \frac{3}{4} \) inch in size to show:

1. DOT-3U.
2. Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.
3. Month and year of manufacture.
4. (Rated) capacity.

§ 178.24-6 [Amended]

24. In § 178.24-6, paragraph (a) is amended by changing the word “chapter” to “subchapter.”

25. In § 178.27-2, paragraph (c) is revised to read as follows:

§ 178.27-2 Construction, capacity and marking.

(c) Marking: Each container must be permanently marked in figures and letters at least \( \frac{3}{4} \) inch in size to show:

The symbol and numbers must be those of person making DOT mark.
must be registered with the Bureau of Explosives.

36. Section 178.140-5 is revised to read as follows:

§ 178.140-6 Marking.
(a) Marking on each container by embossing on head with raised marks as follows:
(1) DOT-13.
(2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

37. Section 178.141-7 is revised to read as follows:

§ 178.141-7 Marking.
(a) Marking on each container by embossing on head with raised marks as follows:
(1) DOT-13A.
(2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

38. In § 178.150-7, paragraph (a) (3) is deleted and paragraph (a) (2) is revised to read as follows:

§ 178.150-7 Marking.
(a) Each container must be marked as follows:
(1) DOT-33A.
(2) The letters "NRC", located just above or below the DOT mark, to indicate a nonhazardous container.
(3) Name or symbol of person making the other marks specified in this section and located on the same face as those other marks. Symbol, if used, must be registered with the Bureau of Explosives.
(4) Size of markings: Specification markings prescribed in this section must be at least (% 1/4 inch high. All markings must be legible.

39. In §§ 178.165-13, 178.176-6, 178.177-6, and 178.171-11, paragraph (a) (1) is deleted and a new paragraph (b) is added to read as follows:

§ 178.165-13, 178.176-6, 178.177-6, and 178.171-11 Marking.
(b) The name or symbol of person making the mark specified in paragraph (a) (1) of this section is revised to read:

§ 178.165-13, 178.176-6, 178.177-6, and 178.171-11, paragraph (a) (1) is deleted and a new paragraph (b) is added to read as follows:

§ 178.194-6 Marking.
(a) Each container must be marked to show:
(1) DOT-29.
(2) The name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.172-19 [Amended]

41. In § 178.172-19, the second sentence in paragraph (a) (1) is deleted and a new paragraph (b) is added to read as follows:

§ 178.172-19
(a) Each container must be marked to show:
(1) DOT-12E110.
(2) This marking shall be enclosed by a rectangle.
(3) Name and address or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

42. In §§ 178.185-19 and 178.186-19, the second sentence in paragraph (a) (1) is deleted and paragraph (b) is revised to read as follows:

§ 178.185-19, 178.186-19 [Amended]
(a) The name or symbol of person making the mark specified in paragraph (a) of this section must be located just above, below, or following those marks. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.185-22 [Amended]
In § 178.185-22, paragraph (c) (3) is deleted and paragraph (c) (2) is revised to read as follows:

§ 178.185-22 Special box authorized only when used in conjunction with inside spec. 2U (§ 178.244 of this chapter) polyethylene 5- and 15-gallon cubical containers.

(a) ● ● ● ●
(b) ● ● ● ●
(c) ● ● ● ●
(2) The name or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above, below, or following that mark. Symbol, if used, must be registered with the Bureau of Explosives.

43. In § 178.185-22, the existing text is designated paragraph (a) and a new paragraph (b) is added to read as follows:

§ 178.187-5 Marking authorized.
• ● ● ●
(1) The name or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above, below, or following that mark. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.212-6 [Amended]
In § 178.212-6, the last sentence in paragraph (a) (1) is deleted and paragraph (a) (2) is revised to read as follows:

§ 178.224-4 Marking.
(a) ● ● ● ●
(b) The name or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above, below, or following those marks. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.225-3 [Amended]
In § 178.225-3, the last sentence in paragraph (a) (1) is deleted.

51. In § 178.226-4, the existing text is designated paragraph (a) and a new paragraph (b) is added to read as follows:

§ 178.226-4 Marking.
(a) Each container must be marked to show:
(1) DOT-29.
(2) The name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

52. In §§ 178.230-3, 178.233-9, 178.234-9, and 178.236-10, the semicolon and text following the DOT specification (for example, DOT-36A) in paragraph (a) (1) is deleted and paragraph (a) (2) is revised to read as follows:

§ 178.230-12 Marking.
(a) Each container must be marked to show:
(1) DOT-36A.
(2) Name and address or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

53. In §§ 178.230-3, 178.233-9, 178.234-9, and 178.236-10, the semicolon and text following the DOT specification (for example, DOT-36A) in paragraph (a) (1) is deleted and paragraph (a) (2) is revised to read as follows:

§ 178.230-12 Marking.
(a) Each container must be marked to show:
(1) DOT-36A.
(2) Name and address or symbol of person making the mark specified in paragraph (a) (1) of this section and located above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.
(a) (2) are deleted and a new paragraph (b) is added to read as follows: Each bag must also be marked with the name and address or symbol of the person making the mark specified in paragraph (a) of this section and be located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

55. Section 178.350-3 is revised to read as follows: § 178.350-3 Marking.

(b) The letter and number size and additional marking requirements of § 172.24 of this subchapter must be complied with.

PART 179—SPECIFICATIONS FOR TANK CARS

57. In Part 179, the authority citation following the table of contents is revised to read as follows: * * * * *

PART 1033—CAR SERVICE

58. Section 179.1 is revised to read as follows: § 179.1 General.

(a) This part prescribes the specifications for tanks that are to be mounted on or form part of a tank car and which are used for the transportation of hazardous materials that require tank cars. (b) Except as provided in paragraph (c) of this section, tanks to which this part is applicable, must be built to the specifications prescribed in this part.

(c) Tanks built to specifications prescribing those in this part may continue in use as provided in § 173.31 of this subchapter.

(d) Any person who performs a function prescribed in this part, shall perform that function in accordance with this part.

(e) When this part requires a tank to be marked with a DOT specification (for example, DOT-105A100W), compliance with that requirement is the responsibility of the tank builder. Marking the tank with the DOT specification shall be understood to certify compliance by the builder that the functions performed by the builder, as prescribed in this part, have been performed in compliance with this part.

(f) The tank builder should inform each person to whom that tank is transferred of any specification requirements which have not been met at time of transfer.

(c) Effective date: This amendment is effective on January 3, 1976.

(49 U.S.C. 1893, 1894, 1816 and 49 CFR 1.53 (e).)


JAMES T. CURTIS, JR.
Director, Materials Transportation Bureau.

[FR Doc. 76-26760 Filed 9-8-76; 8:45 am]

CHAPTER XI—INTERSTATE COMMERCE COMMISSION

SUBCHAPTER A—GENERAL RULES AND REGULATIONS

PART 1033—CAR SERVICE

[Fifth Revised S.O. No. 1234]

Distribution of Freight Cars

September 3, 1976.

At a Session of the Interstate Commerce Commission, Railroad Service Board, held in Washington, D.C., on the 3rd day of September, 1976.

It appearing, That there is an acute shortage of freight cars for transporting shipments of fertilizer, phosphatic, dried or ground, treated or untreated fish meal, grain, grain products, soybeans or soybean products; that certain tariff provisions require the use of smaller cars to transport shipments of such weights; and that such cars cannot be used because of certain tariff provisions; that there is immediate need to use every available car for transportation of fertilizer and grain; that the inability of the carriers to furnish sufficient fertilizer and grain cars results in great economic loss; and that present regulations and practices with respect to the use, supply, control, movement, and distribution of fertilizer and grain cars are general, it is the opinion of the Commission that an emergency exists requiring immediate action to promote car service in the interest of the public and the commerce of the people. Accordingly, the Commission finds that notice and public procedure are impracticable and contrary to the public interest, and that good cause exists for making this order effective upon less than thirty days' notice.

It is ordered, That:

§ 1033.1234 Distribution of freight cars.

(a) Subject to the concurrence of the shipper, carriers may substitute a sufficient number of smaller cars for larger cars ordered to transport shipments of fertilizer, phosphatic, dried or ground, treated or untreated, fish meal, grain, grain products, soybeans or soybean products regardless of tariff requirements specifying minimum cubic or weight carrying capacity. (See exceptions (b) and (c).)

(b) Exception. This order shall not apply to shipments subject to tariff provisions requiring the use of twenty-five or more cars per shipment.

(c) match. This order shall not apply to shipments subject to tariff provisions which require that cars be furnished by the shipper.

(d) Rates and minimum weights applicable. The rates to be applied and the minimum weights applicable to shipments for which cars smaller than those ordered have been furnished and loaded as authorized by Section (a) of this order shall be the rates and minimum weights applicable to the larger cars ordered.

(e) Billing to be endorsed. The carrier substituting smaller cars for larger cars as authorized by Section (a) of this order shall place the following endorsement on the bill of lading and on the waybills authorizing movement of the car:

"Car of (------ cu. ft and of (------ ) lb. or greater) is ordered. Smaller cars furnished authority Fifth Revised ICC Service Order No. 1234."

(f) Concurrency of shipper required. Smaller cars shall not be furnished in lieu of cars of greater capacity without the concurrence of the shipper.

(g) Exceptions. Exceptions to this order may be authorized by the Railroad Service Board, Washington, D.C. 20423. Requests for such exceptions must be submitted in writing, or confirmed in writing, and must clearly state the points at which such exceptions are requested and the reason therefor.

(h) Rates and regulations suspended. The operation of all rules, regulations, or tariff provisions is suspended insofar as they conflict with the provisions of this order.

(i) Application. The provisions of this order shall apply to intrastate, interstate, and foreign commerce.

(j) Effective date. This order shall become effective at 12:01 a.m., September 3, 1976.

(k) Expiration date. This order shall expire at 11:59 p.m., October 31, 1976, unless otherwise modified, changed, or suspended by order of this Commission.

(Sec. 1, 12, 15, and 17(2), 24 Stat. 373, 583, 834, as amended; 49 U.S.C. 1, 12, 15, and 17(2). Interprets or applies Sec. 1(10-17), 15(4), and 17(2), 54 Stat. 101, as amended; 49 Sec. 1103-1(10-17), 15(4) and 17(2).)

It is further ordered, That a copy of this order and direction shall be served upon the Association of American Railroads, Car Service Division, as agent of all railroads subscribing to the car service and car hire agreement under the terms of this agreement, and upon the American Short Line Railroad Association; and that notice of this order be given to the general public by depositing a copy in the Office of the Secretary of the Commission at Washington, D.C. and by filing it with the Director, Office of the Federal Register.

By the Commission, Railroad Service Board, members Lewis R. Temple, Thomas
The public hunting of big horn sheep on the Cabeza Prieta National Wildlife Refuge, Arizona, is permitted except in those areas designated by signs as closed to hunting. The big horn sheep season extends from December 4 through December 19, 1976, inclusive. The open big horn sheep area, comprising 846,530 acres, is delineated on maps available at refuge headquarters, Yuma, Arizona, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State regulations covering the hunting of big horn sheep subject to the following special conditions:

1. Bighorn sheep limited to 4 permits issued by the Arizona Game and Fish Department.

2. Bighorn sheep hunters may hunt in those areas designated on their permit.

3. Possession or transportation of any loaded firearm or a dwelling or on motorized vehicle or its attachments is prohibited. A loaded firearm shall mean any firearm containing any ammunition in its chamber, magazine or clip.

4. Possession or transportation of any unsecured firearm in any vehicular or on motorized vehicle or its attachments is prohibited. An unsecured firearm shall mean any firearm not enclosed in a holster, scabbard, or gun case (soft or hard).

5. Travel by vehicle is restricted to designated roads and trails designated by the Refuge Manager. Maps showing these designated routes of travel are available to holders of Arizona Game and Fish Department permits to hunt sheep in this area.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through December 19, 1976.

Las Vegas National Wildlife Refuge

The public hunting of big horn sheep on the Las Vegas National Wildlife Refuge, Arizona, is permitted from December 4 through December 19, 1976, inclusive, but only in the Arizona (Unit 16A) portion designated by signs as open to hunting. This open area, comprising 18,500 acres, is delineated on maps available at refuge headquarters, Needles, California, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State regulations covering the hunting of big horn sheep subject to the following special conditions:

1. Only the person holding the permit issued by the Arizona Game and Fish Department to hunt desert bighorn sheep in Unit 16A will be permitted to hunt on the refuge.

2. Hunting is prohibited within one-fourth mile of any occupied dwelling or concession operation.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through December 19, 1976.
The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through October 10, 1976.

W. O. Nelson, Jr.,
Regional Director,
Albuquerque, New Mexico

August 31, 1976.

PART 32—HUNTING

Fish Springs National Wildlife Refuge, Utah

The following special regulation is issued and is effective September 9, 1976.

§ 32.12 Special regulations: migratory game birds, for individual wildlife refuge areas.

UTAH

FISH SPRINGS NATIONAL WILDLIFE REFUGE

The public hunting of ducks, coots, and mergansers on the Fish Springs National Wildlife Refuge, Utah, is permitted from October 2, 1976 through January 2, 1977, inclusive, but only on the area designated by signs as open to hunting. This open area comprises 5,773 acres and is delineated on maps available at refuge headquarters, 66 miles southwest of Duchy, Utah 89908. Hunting shall be in accordance with applicable State and Federal regulations covering the hunting of ducks, coots, and mergansers, subject to the following special conditions:

(1) All hunters must register at the Visitor Information Station prior to hunting each day, and check out at the end of each day.

(2) Shooting from, upon, or across dikes or roads is prohibited.

(3) The use of small boats, canoes, etc., is permitted during the hunting season, but outward motors or air-thrust boats are prohibited.

(4) Dogs may be used for hunting, but are to be kept under control at all times.

The provisions of these special regulations supplement the regulations that govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through January 2, 1977.

Rolf H. Kraut,
Refuge Manager, Fish Springs National Wildlife Refuge.

August 31, 1976.

(Fr Doc No. 76-20332 Filed 9-8-76; 8:45 am)

PART 32—HUNTING

Certain National Wildlife Refuges in California

The following regulations will be effective October 9, 1976. These regulations apply to public hunting on portions of certain national wildlife refuges in California.

General Conditions: Hunting shall be in accordance with applicable State and Federal regulations. Portions of refuge, which are open to hunting are designated by signs and/or delineated on maps. Special regulations as fire arms, for individual National Wildlife Refuges are listed on the reverse side of maps available at the refuge headquarters and from the office of the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 3777, Portland, Oregon 97208.

§ 32.12 Special regulations: migratory game birds, for individual wildlife refuge areas.

Migratory game birds, except snipe and pheasants and doves, may be hunted on the following refuge areas:

CALIFORNIA

Salton Sea National Wildlife Refuge, P.O. Box 247, Calipatria, California 92233.

Kern National Wildlife Refuge, P.O. Box 319, Daiseno, California 93215.

Special conditions: Due to a lack of water, tern may not have a hunting program this year. Hunters are advised to contact the Refuge Manager or office of the Fish and Game Department for up to date information on water and hunting conditions.

San Luis National Wildlife Refuge. (Headquarters: San Luis National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635.)

Migratory game birds, except pheasants, and doves may be hunted on the following refuge areas:

Sacramento National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Colora National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Delcarm National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Sutter National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Kesterson National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635.

San Luis National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635.

Clear Lake National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuge, Route 1, Box 74, Tulalip, California 99134.)

Special conditions: 1. Boats with or without motors are permitted. Inward hunting day, outward boats are prohibited.

2. All decoys, boats, and other personal property must be removed from the refuge at the close of each day.

Klamath National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuge, Route 1, Box 74, Tulalip, California 99134.)

Special conditions: 1. During the first two days of waterfowl season, all hunters 16 years of age and older must have in their possession an entry permit for the controlled hunting unit in which they are hunting.

2. Posted retrieving zones are established on certain hunting unit. Possession of firearms in these retrieving zones is prohibited, except, unloaded firearms may be taken through these zones when necessary to reach or leave hunting area. Decoys may not be set in retrieving zones.

3. Boats with or without motors are permitted. Air-thrust and labored water-thrust boats are prohibited.

4. All boats, and other personal property must be removed from the refuge at the close of each day.

5. Bow hunters must follow the same regulations as firearm hunters. The use of long bow is permitted.
6. Legal waterfowl shooting hours shall be from one-half hour before sunrise to 1:00 p.m. daily on all California portions of the refuge.

Tule Lake National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuge, Route 1, Box 74, Tulelake, California 96134).

Special conditions: 1. During the first two days of waterfowl season, all hunters 16 years of age and older must have in their possession an entry permit for the controlled hunting unit in which they are hunting.
2. Posted retrieving zones are established on certain hunting units. Possession of firearms in these retrieving zones is prohibited except, unloaded firearms may be taken through these zones when necessary to reach or leave hunting areas. Decoys may not be set in retrieving zones.
3. Boats with or without motors are permitted. Air-thrust and inboard water-thrust boats are prohibited.
4. All decoys, boats, and other personal property must be removed from the refuge at the close of each day.
5. In designated spaced blind areas, hunters may not possess any loaded firearm further than 100 feet from the established blind stakes. Hunters will select blind sites by lottery at the beginning of each day’s hunt. Hunters may shoot only from within their assigned blind sites.
6. The use of long bow is permitted. Bow hunters must follow the same regulations as firearm hunters.
7. Legal waterfowl shooting hours shall be from one-half hour before sunrise to 1:00 p.m. daily.

Modoc National Wildlife Refuge, P.O. Box 1610, Alturas, California 96101.

Special conditions: 1. First weekend only, entry permits are required to enter the hunting area for every individual with the exception of persons under 16 years of age.
2. After first weekend, hunting permitted on Tuesdays, Thursday, and Saturdays during authorized seasons.
3. Hunters are required to enter hunting area via designated parking sites.
4. Hunting area is open for access from 90 minutes prior to legal shooting hours until 90 minutes after sunset on days hunting is permitted.

§ 32.22 Special regulations; upland game; for individual wildlife refuge areas.

Ring-necked pheasant only may be hunted on the following refuge areas:

CALIFORNIA

Colusa National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.
Delavan National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.
Kern National Wildlife Refuge, P.O. Box 219, Delano, California 93215.

Special condition: Due to a lack of water, Kern may not have a hunting program this year. Hunters are advised to contact the Refuge Manager or office of the California Fish and Game Department for up to date information on water and hunting conditions.

Merced National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635.

Sacramento National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.
Sutter National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.
Lower Klamath National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuge, Route 1, Box 74, Tulelake, California 96134).

Special conditions: 1. Additional refuge area designated by special posting will be open to a special 4-day pheasant hunt.
2. Pheasants may not be hunted in retrieving zones.
3. Daily limit is two male pheasants during the Special Hunt.

Tule Lake National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuge, Route 1, Box 74, Tulelake, California 96134).

Special conditions: 1. Additional refuge area designated by special posting will be open to a special 4-day pheasant hunt.
2. Pheasants may not be hunted in retrieving zones.
3. Daily limit is two male pheasants during the Special Hunt.

The provisions of these special regulations supplement the regulations which govern hunting on wildlife refuge areas generally and which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through June 30, 1977.

JAMES W. TITLER, Regional Director, Fish and Wildlife Service.

[FED.Reg.76-26290 Filed 9-8-76;8:45 am]
DEPARTMENT OF THE TREASURY
Customs Service
AIR COMMERCIAL REGULATIONS
Landing Requirements for Private Aircraft Arriving From Areas South of the United States

In order to provide better Customs service to private aircraft arriving from certain areas south of the United States, it is considered desirable to add the Presidio-Lely International Airport, Presidio, Texas, to the list of designated airports set forth in § 6.14(e) of the Customs Regulations (19 CFR 6.14(e)).

Accordingly, notice is hereby given that under the authority of 19 U.S.C. 581, as amended (19 U.S.C. 66), section 626, 49 Stat. 759 (19 U.S.C. 1624), and section 1108, 72 Stat. 799, as amended (49 U.S.C. 1608), it is proposed to amend § 6.14(e) of the Customs Regulations (19 CFR 6.14(e)) by adding the Presidio-Lely International Airport, Presidio, Texas, to the list of designated airports for private aircraft arriving from certain areas south of the United States.

Prior to the adoption of the foregoing proposal, consideration will be given to any relevant data, views, or arguments which are submitted in writing to the Commissioner of Customs, Attention: Regulations Division, Washington, D.C. 20229, and received not later than September 24, 1976.

Written material and suggestions submitted will be available for public inspection in accordance with section 16.8(b) of the Customs Regulations (19 CFR 16.8(b)), at the Regulations Division, Headquarters, United States Customs Service, Washington, D.C., during regular business hours.

VERNON D. ACREE,
Commissioner of Customs.

Approved: September 1, 1976.

DANIEL R. MC DONALD,
Assistant Secretary of the Treasury.

Office of the Secretary
DISCLOSURE OF RECORDS
FEES FOR SERVICES

The Department of the Treasury proposes to amend its regulations at 31 CFR Part 6, governing fees for services rendered in connection with the disclosure of records. The proposed amendments are to the regulations issued pursuant to 5 U.S.C. 552, as amended (the Freedom of Information Act); however, pursuant to 31 CFR 1.26, the amendments would also affect the fees to be charged for requests made under the Privacy Act of 1974. The purpose of the amendments is to more closely conform to the Freedom of Information Act, by eliminating minimum fees; to make the fee charged for locating records under FOIA to a level which more closely approximates the cost of the service rendered and to eliminate the imposition and collection of fees when the charges would be minimal.

Accordingly, notice is hereby given pursuant to 5 U.S.C. 553 that the Department of the Treasury proposes, pursuant to the authority of 5 U.S.C. 552(a), (4) (A) and 21 U.S.C. 485a, to adopt the following amendments to Part 1, Subtitle A of Title 31 of the Code of Federal Regulations:

§ 1.6 [Amended]
1. Revise § 1.6(g) (1) (I) and (g) (3) (I) to read:
   (I) Photographs, per page up to 8 1/2" x 14", 50.10 each, except that no charge shall be imposed for copying 10 pages or less...
   (II) The fee charged for services of personnel involved in locating records shall be $5.00 for each hour or fraction thereof, except that no charge shall be imposed for a search consuming one hour or less.
   2. Amend § 1.6(g) (3) (II) by changing "$3.50" to read "$5.00."

Interested persons are invited to submit written comments, suggestions or objections regarding the above amendments to Richard R. Albrecht, General Counsel, Room 3008, Department of the Treasury, Washington, D.C. 20229, on or before October 12, 1976. Comments submitted in response to this Notice will be available to the public upon request therefor.


RICHARD R. ALBRECHT,
General Counsel.

DEPARTMENT OF AGRICULTURE
AGRICULTURAL MARKETING SERVICE
FILBERTS GROWN IN OREGON AND WASHINGTON
Proposed Grade Regulations for Shelled Filberts

Notice is given of proposals to (1) establish minimum grade regulations for shelled filberts, (2) change the grade requirement prescribed for shelled filberts declared and withheld in lieu of merchantable filberts in satisfaction of a restricted obligation; and (3) make a conforming change in the administrative rules and regulations. This action is pursuant to the marketing agreement, as amended, and Order No. 832, as amended (7 CFR Part 982; 20 FR 55250, 55933), regulating the handling of filberts grown in Oregon and Washington.

It is necessary to establish these standards because of the continuing importance of the shelled filbert market. Mandatory inspection and certification of filbert kernels would tend to promote orderly marketing because only acceptable quality kernels could be handled, and consumers and users could depend on the quality of each shipment.

This proposal would also necessitate a change in the standards applied to shelled filberts declared and withheld by a handler in lieu of merchantable filberts in satisfaction of a restricted obligation pursuant to §§ 932.50(a) and 932.51(b). Section 932.50(a) currently provides that these shelled filberts should meet the standards in effect for Oregon No. 1 grade for shelled filberts as contained in Oregon Grade Standards for Filbert (Hazelnut) Kernels, or such other standards as may be recommended by the Board and established by the Secretary. Because of its recommendation to establish minimum grade regulations for shelled filberts, the Board also recommended, as a conforming change, the establishment of this grade for shelled filberts declared and withheld in lieu of merchantable filberts in satisfaction of a restricted obligation.

Both proposals would be included in § 982.101 of a new subpart entitled Subpart—Grade and Size Regulation. It is also proposed that the reference to "Oregon Grades and Standards for Walnuts and Filberts" in § 932.453 of Subpart—Administrative Rules and Regulations (7 CFR 932.453-932.471) be changed to "Oregon Grade Standards for Walnuts and Filberts."
Filberts In Shell." This is a conforming change to recognize a change in the title of the standards applicable under the order to inshell filberts.

Consideration will be given to any written data, views, or arguments pertaining to the proposal which are received by the Hearing Clerk, U.S. Department of Agriculture, Room 112, Administration Building, Washington, D.C. 20250, not later than September 22, 1976. All written submissions made pursuant to this notice should be mailed quadruplicate and will be made available for public inspection at the office of the Hearing Clerk during official hours of business (7 CFR 1.27(b)). The proposals follow:

Subpart—Grade and Size Regulation

1. Add a new subpart entitled Subpart—Grade and Size Regulation and include a § 982.101 in that subpart reading as follows:

§ 982.101 Minimum grade standards for shelled filberts.

(a) Pursuant to § 982.50(a), no handler shall handle any shelled filberts unless such filberts meet the requirements for Oregon No. 1 whole and broken grade for shelled filberts as contained in Oregon Grade Standards for Filbert (Hazelnut) Kernels.

(b) Pursuant to § 982.50(a) and 982.51(b), a handler may declare and withhold shelled filberts in lieu of merchantable filberts in satisfaction of his restricted obligation. Shelled filberts so declared and withheld shall, in lieu of the standards prescribed pursuant to § 982.50(a) (3), meet the standards in effect for Oregon No. 1 whole and broken grade for shelled filberts as contained in Oregon Grade Standards for Filbert (Hazelnut) Kernels.

2. In § 982.453 of Subpart—Administrative Rules and Regulations (7 CFR 982.452—982.471), "Oregon Grades and Standards for Walnuts and Filberts" is revised to read "Oregon Grade Standards Filberts In Shell."
PEOPOSED RULES

[24 CFR Part 1917]

[DOcket No. FE-2296]

APPEALS FROM FLOOD ELEVATION DETERMINATION AND JUDICIAL REVIEW

Proposed Flood Elevation Determinations for the City of Riverside, Missouri


Under these Acts, the Administrator, to whom the Secretary has delegated the statutory authority, must develop criteria for flood plain management in identified flood hazard areas. In order to partici-
PROPOSED RULES

It is the agency's present view that aspects of each system can be adapted to serve the needs of all VIN users. Specifically, the NHTSA is considering a vehicle descriptor composed of a fixed field of six characters, with the manufacturer option to fill each position in the field with a character that has meaning or with a character that the position is blank. In this way, a fixed-length VIN is achieved in the interests of transcription accuracy. The agency believes that transcription accuracy will contribute to motor vehicle safety by aiding research in motor vehicle accident causation and the recall of defective or non-complying vehicles. At the same time, manufacturers would retain flexibility in the number of meaningful characters they wish to utilize, permitting the continued use of existing codes and computer capacity.

The one-time costs of adopting any standardized system are solicited as the grounds for an agency decision on the reasonableness of proposing this change. Particular costs or complexity associated with extending the standard's applicability to all types of motor vehicles (i.e., trucks, buses, multipurpose passenger vehicles, trailers) would also need to be noted. Comments on anticipated lead times are also requested.

The views of all interested parties, particularly vehicle manufacturers, component suppliers, data processing specialists, vehicle administrators, insurance companies, and law enforcement officials, are solicited. It is anticipated that a public meeting to consider all issues raised by this notice will take place shortly after the comment closing date. To assist in the development of written and oral comments, a summary of the ISO and VESC systems follows.

The ISO VIN has a variable length of 12 to 17 alpha/numeric characters (except the last four must be numeric) and must not be identical to another VIN assigned within 30 years.

The ISO VIN consists of three sections:
1. The World Manufacturer Identifier (WMI)—three characters to identify continent, country, and manufacturer.
2. The Vehicle Descriptor Section (VDS)—one to six characters to identify the general attributes of the vehicle.
3. The Vehicle Indicator Section (VIS)—eight characters to identify model year, manufacturing plant, and to provide for assignment of a sequential number.

The VESC VIN consists of two regulations published in 1976 to establish a system for passenger cars and non-motive powered recreational vehicles. This VIN specifies a fixed length of 15 characters. The informational content and type of each character is specified, except that year and character are made of six roman letters or arabic numerals.

The format of the VESC VIN consists of two sections:
1. Vehicle Descriptor Section (VDS)—seven characters to describe the vehicle. For passenger cars this is a three character make identifier followed by car line, series, body type and engine type identifiers.

2. Vehicle Indicator Section (VIS)—eight characters to indicate model year, manufacturing plant and to provide for assignment of sequential number. The descriptors section to be four alpha characters. The descriptor requires at least one and permits up to six alpha or numeric characters in its descriptor section. Comments are requested concerning possible ways of resolving the differences between the two systems.

It is noted that the Volkswagen and MVMA petitions, which both request adoption of standardization in accordance with the ISO standard, will be granted or denied on the basis of the agency's future decision on a specific course of action.

Interested persons are invited to submit information, views, and arguments on the areas described and on the general subject of VIN standardization. Comments should refer to the docket number and be submitted to: Docket Section, National Highway Traffic Safety Administration, Room 5108, 400 Seventh Street, SW., Washington, D.C. 20590. It is requested but not required that 10 copies be submitted.

All comments received before the close of business on the comment closing date indicated below will be considered, and will be available for examination in the docket at the above address both before and after that date. The NHTSA will continue to file relevant material as it becomes available in the docket after the closing date, and it is recommended that interested persons continue to examine the docket for new material.

Environmental Protection Agency

[40 CFR Part 52]

APPROVAL AND PROMULGATION OF IMPLEMENTATION PLANS

Plan Revisions—Montana

On May 5, 1976, the Governor of Montana submitted proposed revisions to the Montana State Implementation Plan (SIP). These revisions amend regulations applicable to incinerators, industrial processes, petrochemical processes, the control of odors, and aluminum reduction facilities (Anaconda Aluminum Company); and provides for new procedures relating to violations of emission standards caused by malfunctions. Adequate funds have been set aside for the revision. Federal new source performance standards as State regulations.

Revisions Applicable to Anaconda Aluminum

On May 5, 1976, the Governor of Montana submitted regulation 16-2.14(1)—S1430, a general regulation for industrial processes, which relate allowable emissions to the process weight. Because of the difficulty in defining specific process weights at aluminum reduction facilities, this provision was rendered unenforceable as a practical matter against this source.

On December 1, 1976, the Governor of Montana completed the May 5, 1976 SIP package by submitting a compliance schedule setting forth a timetable by which Anaconda will come into compliance with regulation S1430. The schedule includes incremental steps toward compliance with the emission limitation. The Anaconda Aluminum Company shall be in full compliance by June 1, 1979, with all applicable Montana laws and regulations on fluoride and particulate emissions from the company's aluminum reduction plant at Columbus Falls, Montana. The final control plan is designed to provide for attainment of the national ambient air quality standards for particulate matter as expeditiously as practicable in the vicinity of the aluminum reduction plant.

Miscellaneous Revisions

On September 4, 1976, the Governor of Montana submitted various revisions to the SIP. The revisions consist of the following changes to the presently approved SIP:

Industrial Processes (16-2.14(1)—S1430): This revision indicates that reduction cells of a primary aluminum reduction plant and sources subject to the New Source Performance Standards listed in Montana Administrative Code regulation 16-2.14(1)—S14083 will not be subject to regulation 16-2.14(1)—S1430, Particulate Matter, Industrial Processes since specific state regulations are in effect for these facilities.

Incinerators (16-2.14(1)—S1430): The presently approved SIP requires all incinerators to limit particulate matter emissions to 0.2 grams per standard cubic foot of dry flue gas. The proposed revision requires all new incinerators (constructed or modified after September 5, 1979) to limit particulate matter emissions to 0.10 grams per standard cubic foot of dry flue gas.
cept that all new incinerators subject to the New Source Performance Standards set forth at 40 CFR Part 60 shall meet those Federal standards. Additionally, all existing incinerators must meet a particulate matter emission standard of 0.10 grains per standard cubic foot of dry gas by September 30, 1977. Further, all incinerators must comply with a 10 percent opacity limitation. These provisions would effectively curtail overall particulate emissions from incinerators.

Storage of Petroleum Products (16-2.14(1)-S14070): The proposed revision adds crude oil to the list of petroleum products which are subject to the storage requirements. The proposed revision also exempts from the regulation existing refineries which normally process less than 7000 barrels per day of crude oil. In addition, the proposed revision extends the date for final compliance with the storage requirements from June 30, 1972 to January 1, 1977 for those refineries which normally process 7000 barrels per day or more of crude oil. These provisions would not result in an increase in emissions from existing installations.

Control of Odors (16-2.14(1)-S1480): The proposed revision no longer exempts equipment used to process food for human consumption in food service establishments from the odor regulation. Since odors are not a criteria pollutant under the Clean Air Act, this provision would not be considered a part of the SIP.

Malfunction Regulation (16-2.14(1)-S14000): So called malfunction regulations are interpretations of an emission limitation in that they signify how the limitation will be enforced. Therefore, this State malfunction regulation advises the sources of the manner in which the State may exercise its discretion in enforcing the applicable emission limitation.

The proposed revision provides that when a malfunction of equipment causes an increase in emissions which would continue for four (4) hours, the owner or operator must notify the State agency. Application may be made by the owner or operator to continue operation for an extended malfunction of malfunctions. In addition, the State agency may require the owner or operator to submit a written report of the malfunction. The regulation further provides that a source shall be considered in violation of the applicable emission limitation unless the appropriate procedures are followed and enforcement discretion is exercised.

The proposed approved provision provided only for reporting of a malfunction that extended eight (8) hours.

Standards for New Sources (16-2.14(1)-S1400): This regulation incorporates the Federal New Source Performance Standards (40 CFR Part 60) as State Standards for the following source categories: Fossil fuel-fired steam generators; incinerators; coking plants; nitric acid plants; sulfuric acid plants; asphalt concrete plants; petroleum refineries; storage vessels for petroleum; asphalt concrete plants; secondary brass and bronze ingot processing plants; iron and steel plants; and sewage treatment plants.

Preliminary review indicates that EPA intends to approve all the revisions as submitted by Montana. The proposed revisions are available for public inspection at the office of the State agency and at the offices of the Environmental Protection Agency listed below.

Department of Health and Environmental Sciences, Environmental Sciences Division, Air Quality Bureau, Cogswell Building, Helena, Montana 59601.

Environmental Protection Agency, Region VIII, Office of Public Affairs, Suite 550, 1620 Lincoln Street, Denver, Colorado 80203.

Environmental Protection Agency, Region VIII, Office of Air Programs, 420 M Street, S.W., Washington, D.C. 20460.

Interested persons are encouraged to submit written comments on any of the proposed revisions. Such comments will be accepted for consideration until October 12, 1976. Comments should be addressed to the Office of Regional Counsel, Environmental Protection Agency, Region VIII, Suite 500, 1620 Lincoln Street, Denver, Colorado 80203.

Dated: August 16, 1976.

John A. Green, Regional Administrator.

It is proposed to amend Part 59 of Chapter I, Title 40 of the Code of Federal Regulations as follows:

Subpart BB—Montana

In § 52.1383, the table is amended as follows:

§ 52.1383 Compliance schedules.

<table>
<thead>
<tr>
<th>Source Location</th>
<th>Date of Effective date</th>
<th>Final compliance date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1977-1-1</td>
<td></td>
</tr>
</tbody>
</table>

[40 CFR Part 55]

[FR Doc. 82-18828 Filed 8-8-76:8:45 am]

ENERGY RELATED AUTHORITY UNDER SECTION 119 OF THE CLEAN AIR ACT

Withdrawal of Proposed Compliance Date Extension for Niagara Mohawk Power Corporation, New York State

The purpose of this Federal Register notice is for the Environmental Protection Agency (EPA) to announce withdrawal of its proposed compliance date extension for the Niagara Mohawk Power Corporation, Albany Station, Units 1, 2, 3 and 4. This regulatory action was proposed by EPA under the authority of section 119 of the Clean Air Act on March 30, 1976 (41 FR 13371) and revised on June 14, 1976 (41 FR 13750).

Section 2 of the Energy Supply and Environmental Coordination Act of 1974 (ESCEA), as amended by the Energy Policy and Conservation Act, authorizes the Administrator of Energy to direct the Environmental Energy Administration (EPA) to issue orders to certain powerplants and major fuel burning installations prohibiting such facilities from burning natural gas or petroleum products as their primary energy source. Section 3 of ESCEA added a new Section 119 to the Clean Air Act which requires the Administrator of the EPA to issue compliance dates for meeting certain air pollution requirements to facilities issued FEA prohibition orders whenever certain eligibility criteria are satisfied.

One such eligibility criterion is the requirement of section 119(c) (2) (C) of the Clean Air Act that facilities receiving compliance date extensions must achieve the most stringent degree of emission limitation in that they signify how the New Source Performance Standards (40 CFR Part 60) as State Standards for the following source categories: Fossil fuel-fired steam generators; incinerators; coking plants; nitric acid plants; sulfuric acid plants; asphalt concrete plants; petroleum refineries; storage vessels for petroleum; asphalt concrete plants; secondary brass and bronze ingot processing plants; iron and steel plants; and sewage treatment plants.

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976

38391

40 CFR Part 55]

[FR Doc. 82-18828 Filed 8-8-76:8:45 am]

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FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976

38391
Proposed Rules

By the Chief, Common Carrier Bureau: Presently before the Commission for consideration is the request of the National Association of Radiotelephone Systems (NARS) for an extension of time for filing comments and reply comments in the above-captioned proceeding. A notice of inquiry and notice of proposed rulemaking in this matter was adopted by the Commission on July 7, 1976 and was released on July 15, 1976 (41 FR 29452, July 16, 1976).

1. NARS states that the broad scope of this proceeding, which is intended in part to formulate "objective" standards for licensing new or additional DPLMRS facilities, necessitates a comprehensive economic investigation of the radio common carrier industry together with a complete revaluation of the substantive and procedural licensing policies of the Commission. Moreover, NARS states the Commission has imposed stringent pleading burdens on those parties who challenge the premises and conclusions expressed or implicit in the notice. Expressing a desire to assist the Commission in its examination of the issues in a systematic and comprehensive fashion, NARS insists that absent and adequate existing data base nor an in-house staff capable of conducting a major inquiry, additional time is required so that NARS might sponsor a study of the industry so as to obtain sufficient specific factual data which would enable NARS to prepare its comments.

2. We have considered all the matters advanced by NARS and agree that the public interest would be served by granting parties additional time in which to file comments in this proceeding. Although we do not agree with NARS that a six-month extension of time is necessary, we will extend for two months the filing dates as specified in the original notice.

3. Accordingly, pursuant to Section 0.303(c) of the Commission's rules, it is ordered, that, to the extent indicated above, the request of the National Association of Radiotelephone Systems, is granted, and the time for filing comments in this proceeding is extended from September 3 to November 5, 1976, and the time for filing reply comments is extended from October 1 to December 3, 1976; and that, in all other respects, this request is denied.

Federal Communications Commission
Joseph A. Marino,
Deputy Chief,
Common Carrier Bureau.

Federal Register, Vol. 41, No. 176—Thursday, September 9, 1976
DEPARTMENT OF DEFENSE
ARME FORCES INSTITUTE OF PATHOLOGY SCIENTIFIC ADVISORY BOARD
Cancellation Meeting
August 30, 1976.
Notice of the meeting of the Armed Forces Institute of Pathology's Scientific Advisory Board, announced in Volume 41, Federal Register, No. 163, on 20 August 1976, at page 35561, scheduled for 16-17 September, 1976, at 0830 hours in the Director's Conference Room, Armed Forces Institute of Pathology, Washington, D.C., is hereby cancelled.
Dated: September 2, 1976.
By authority of the Secretary of the Army.
R. S. Seeker, LTC, U.S. Army Acting Director, Admin. Mgt. Directorate TAGGEN

SPECIAL COMMISSION ON THE UNITED STATES MILITARY ACADEMY
Establishment
In accordance with the provisions of Public Law 92-483, Federal Advisory Committee Act, notice was given on Friday, 3 September 1976, 41 FR 37352, that the Department of the Army would establish the Special Commission on the United States Military Academy. The Office of Management and Budget concurred in its establishment and in the publication of the above stated notice.

The Office of Management and Budget at the request of the Department of Defense has further reviewed the purpose for which the Special Commission on the United States Military Academy is being established and has determined that it is in the best interest of the public that this Commission be established at the earliest possible date. Therefore, the Office of Management and Budget agreed to waive its requirement that the above referenced notice appear in the Federal Register at least 15 days prior to the filing of the Committee's Charter with the appropriate standing Committee's of the Senate and the House of Representatives of the United States Congress. Accordingly, the Committee Management Secretariat of the Office of Management and Budget has authorized the Department of Defense to file the Charter for the Special Commission on the United States Military Academy this date with the Armed Services Committee of the United States Senate, the Armed Services Committee of the United States House of Representatives and the Library of Congress.

Marc R. Roch, Director for Correspondence and Directives, OASD (Comp. I) September 7, 1976.

Office of the Secretary
DEFENSE SCIENCE BOARD TASK FORCE ON PATRIOT VULNERABILITY
Meeting
The Defense Science Board Task Force on PATRIOT Vulnerability will meet in closed session on 28, 29, and 30 September 1976, in the Pentagon, Washington, D.C.

The mission of the Defense Science Board is to advise the Secretary of Defense and the Director of Defense Research and Engineering on overall research and engineering and to provide long-range guidance in these areas to the Department of Defense.

The task force will provide an analysis of the PATRIOT vulnerability to current and projected threats and provide related guidance and advice regarding R&D action considered appropriate within the Department of Defense.

In accordance with Section 10(d) of Appendix I, Title 5, United States Code, it has been determined that this task force meeting concerns matters listed in Section 552(b) of Title 5 of the United States Code, specifically subparagraph (1) thereof, and that accordingly this meeting will be closed to the public.

Marc R. Roch, Director, Correspondence and Directives, OASD (Comp. II) September 3, 1976.

DEPARTMENT OF JUSTICE
Drug Enforcement Administration
MANUFACTURE OF CONTROLLED SUBSTANCES
Application
Section 303(a) (1) of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 823(a) (1)) states: "The Attorney General shall register an applicant to manufacture controlled substances in schedule I or II if he determines that such registration is consistent with the public interest and with United States obligations under international treaties, conventions, or protocols in effect on the effective date of this part. In determining the public interest, the following factors shall be considered:
(1) maintenance of effective controls against diversion of particular controlled substances and any controlled substance in schedule I or II compounded therefrom into other than legitimate medical, scientific, research, or industrial channels, by limiting the importation and bulk manufacture of such controlled substances to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes;"

Pursuant to Section 301 of the Controlled Substances Act (21 U.S.C. 821), and in accordance with 21 CFR 1301.43 (a), notice is hereby given that the above firm has made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic class of controlled substances listed below:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>II</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>II</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>II</td>
</tr>
</tbody>
</table>

Pursuant to Section 301 of the Controlled Substances Act (21 U.S.C. 821), and in accordance with 21 CFR 1301.43 (a), notice is hereby given that the above firm has made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic class of controlled substances as indicated, and any other person, and any existing registered bulk manufacturer of the above substances may file written comments on or objections to the issuance of such registration and may, at the same time, file a written request for a hearing on the application in accordance with 21 CFR 1301.54 in such form as prescribed by 21 CFR 1316.57. Such comments, objections and requests for a hearing may be filed no later than October 14, 1976.

Comments and objections may be addressed to the DEA Federal Register Representative, Office of Chief Counsel, Drug Enforcement Administration, Room 1235, 1455 Eye Street, NW., Washington, DC. 20537.

Dated: August 30, 1976.
MANUFACTURE OF CONTROLLED SUBSTANCES
Application

Section 303(a)(1) of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 823(a)(1)) states: "The Attorney General shall register an applicant to manufacture controlled substances in schedule I or II if he determines that such registration is consistent with the public interest and with United States obligations under international treaties, conventions, or protocols in effect on the effective date of this part. In determining the public interest, the following factors shall be considered:

(1) maintenance of effective controls against diversion of particular controlled substances and any controlled substance in schedule I or II compounded therefrom into other than legitimate medical, scientific, research, or industrial channels, by limiting the importation and bulk manufacture of such controlled substances to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions, medical, scientific, research, and industrial purposes;

Pursuant to Section 1301.43 of Title 21 of the Code of Federal Regulations (CFR), notice is hereby given that the following manufacturers made application to the Drug Enforcement Administration to be registered as bulk manufacturers of the basic class of controlled substances listed below:

Eli Lilly & Co., 1249 South White River Parkway, East Drive, Building 80, Indianapolis, IN 46252 (undated):

Drug: Schedule
Methadone ............................... II
Methadone-Intermediate ........... II

Eli Lilly & Co., 1249 South White River Parkway, East Drive, Building 80, Indianapolis, IN 46252 (undated):

Drug: Schedule
Oxymorphone .......................... II
Secobarbital ............................ II
Amobarbital ............................. II

Pursuant to Section 301 of the Controlled Substances Act (21 U.S.C. 821), and in accordance with 21 CFR 1301.43(a), notice is hereby given that the above firms have made application to the Drug Enforcement Administration to be registered as bulk manufacturers of the basic class of controlled substances indicated, and any other such person, and any existing registered bulk manufacturer of any of the above basic class of controlled substances, may file written comments on or objections to the issuance of such registrations and may at the same time request for a hearing on the applications in accordance with 21 CFR 1301.54 in such form as prescribed by 21 CFR 1316.47. Such comments, objections and requests for a hearing may be filed no later than October 14, 1976.

Comments and objections may be addressed to the DEA Federal Register Rep-representative, Office of Chief Counsel, Drug Enforcement Administration, Room 1203, 1405 Eye Street, NW, Washington, D.C. 20537.

Dated: August 30, 1976.

JERRY N. JENSON,
Deputy Administrator,
Drug Enforcement Administration.

[FR Doc. 76-23314 Filed 9-8-76; 8:45 am]

MANUFACTURE OF CONTROLLED SUBSTANCES
Application

Section 303(a)(1) of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 823(a)(1)) states:

The Attorney General shall register an applicant to manufacture controlled substances in schedule I or II if he determines that such registration is consistent with the public interest and with United States obligations under international treaties, conventions, or protocols in effect on the effective date of this part. In determining the public interest, the following factors shall be considered:

(1) maintenance of effective controls against diversion of particular controlled substances and any controlled substance in schedule I or II compounded therefrom into other than legitimate medical, scientific, research, or industrial channels, by limiting the importation and bulk manufacture of such controlled substances to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions, medical, scientific, research, and industrial purposes;

Pursuant to Section 1301.43 of Title 21 of the Code of Federal Regulations (CFR), notice is hereby given that on August 18, 1976, Pharmaceuticals Division, Ciba-Geigy Corp., 556 Morris Avenue, Summit, N.J. 07901, made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of methylphenidate, a basic class of controlled substance in schedule II.

Pursuant to Section 301 of the Controlled Substances Act (21 U.S.C. 821), and in accordance with 21 CFR 1301.43(a), notice is hereby given that the above firms have made application to the Drug Enforcement Administration to be registered as bulk manufacturers of the basic class of controlled substances indicated, and any other such person, and any existing registered bulk manufacturer of any of the above basic class of controlled substances, may file written comments on or objections to the issuance of such registrations and may at the same time request for a hearing on the applications in accordance with 21 CFR 1301.54 in such form as prescribed by 21 CFR 1316.47. Such comments, objections and requests for a hearing may be filed no later than October 14, 1976.

Comments and objections may be addressed to the DEA Federal Register Representative, Office of Chief Counsel, Drug Enforcement Administration, Room 1203, 1405 Eye Street, NW, Washington, D.C. 20537.

Dated: August 30, 1976.

JERRY N. JENSON,
Deputy Administrator,
Drug Enforcement Administration.

[FR Doc. 76-23314 Filed 9-8-76; 8:45 am]
NOTICES

WASHINGTON, D.C.
F and Wildlife Service issued a permit pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969, the Department of the Interior has issued a final environmental statement for the proposed Eastern New Mexico Water Supply Project, New Mexico.

Notice of Availability of Final Environmental Statement
Pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969, the Department of the Interior has prepared a final environmental statement for the proposed Eastern New Mexico Water Supply Project, New Mexico. The environmental statement concerns a proposed 548-mile aqueduct to deliver municipal and industrial water from the Reservoir to nine project cities in Eastern New Mexico.

Copies are available for inspection at the following locations:

Single copies of the final statement may be obtained on request to the following:
Ronald G. Coleman, Assistant Secretary of the Interior.

DEPARTMENT OF AGRICULTURE

Farmers Home Administration
Notice of Designation No. 4370

FLORIDA
Designation of Emergency Areas
The Secretary of Agriculture has determined that certain areas in Florida have been substantially affected by drought and the provisions of the Consolidated Farm and Rural Development Act, as amended by Public Law 94-105, as a result of excessive rainfall through June 15, 1976.

Therefore, the Secretary has designated the area as eligible for emergency loans pursuant to the provisions of the Consolidated Farm and Rural Development Act, as amended by Public Law 94-68, and the provisions of 7 CFR 1832.3(b) including the recommendation of Governor Reubin O'D. Askew that such designation be made.

Applications for emergency loans must be received by this Department no later than August 1, 1976, for physical losses in Young County, Texas, as a result of prolonged drought during August 1, 1976, through May 24, 1976.

Therefore, the Secretary has designated this area as eligible for emergency loans pursuant to the provisions of the Consolidated Farm and Rural Development Act, as amended by Public Law 94-68, and the provisions of 7 CFR 1832.3(b) including the recommendation of Governor Dolph Briscoe that such designation be made.

Applications for emergency loans must be received by this Department no later than October 20, 1976, for physical losses in Sumter County, Florida, as a result of successive rainfall May 15 through June 15, 1976.

Therefore, the Secretary has designated the area as eligible for emergency loans pursuant to the provisions of the Consolidated Farm and Rural Development Act, as amended by Public Law 94-68, and the provisions of 7 CFR 1832.3(b) including the recommendation of Governor Reubin O'D. Askew that such designation be made.

Applications for emergency loans must be received by this Department no later than October 20, 1976, for physical losses in May 16, 1977, for production losses, except that qualified borrowers who receive initial loans pursuant to this designation may be eligible for subsequent loans. The urgency of the need for loans in the designated area makes it impracticable and contrary to the public interest to give advance notice of proposed rulemaking and invite public participation.

Done at Washington, D.C., this 1st day of September, 1976.

Joseph R. Hanson, Acting Administrator, Farmers Home Administration.

[FR Doc.76-26310 Filed 9-8-76;8:45 am]

Forest Service
Proposed Addition to the Teton Wilderness
Notice of Availability of Draft Environmental Statement
Pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969, the Forest Service, Department of Agriculture, has prepared a draft environmental statement for the proposed addition to the Teton Wilderness, Bridger-Teton National Forest, Wyoming.

The Forest Service report number is USDA-FS-DES (Leg) 76-09.

The environmental statement evaluates the proposal to increase the Teton Wilderness from 557,311 to 588,629 acres by moving the present boundary...
westward to the border of the John D. Rockefeller, Jr. Memorial Parkway and Grand Teton National Parks. Present management has been limited to non-consumptive uses, chiefly recreation and watershed protection. The area is similar in character to the adjoining Teton Wilderness. Its location, in the heart of a very large area dedicated to recreation and preservation of natural ecosystems, makes the area highly sensitive to any management which would sharply conflict with the goals and philosophy of the surrounding areas.

This proposed addition of 20,318 acres to the existing Teton Wilderness would be administered to the existing Teton Wilderness would be administered to the existing Teton Wilderness and the surrounding areas.

Part of the area proposed for classification as wilderness would conflict with the goals and philosophy of the adjoining Teton Wilderness. This large area dedicated to recreation and preservation of natural ecosystems, makes the area highly sensitive to any management which would sharply conflict with the goals and philosophy of the surrounding areas.

This is a very large area dedicated to recreation and preservation of natural ecosystems, making the area highly sensitive to any management which would sharply conflict with the goals and philosophy of the surrounding areas.

This draft environmental statement was transmitted to CEQ on September 2, 1976.

Copies are available for inspection during regular working hours at the following locations:

USDA, Forest Service, South Agriculture Building, Room 2330, 12th & Independence Ave., SW., Washington, D.C. 20250.

Regional Planning Office, USDA, Forest Service, Federal Building, Room 4408, 324 2nd Street, Ogden, Utah 84401.

Forest Supervisor, Teton National Forest, Forest Service Building, P.O. Box 1888, Jackson, Wyoming 83001.

A limited number of single copies are available upon request to John R. McGuire, Chief, Forest Service, South Agriculture Building, 12th and Independence Avenue, SW., Washington, D.C. 20250 and/or H. Reid Jackson, Forest Supervisor, Forest Service Building, P.O. Box 1888, Jackson, Wyoming 83001.

Copies of the environmental statement have been sent to various Federal, State, and local agencies as outlined in the CEQ guidelines.

Comments are invited from the public and from State and local agencies which are authorized to develop and enforce environmental standards and from Federal agencies having jurisdiction or special expertise with respect to any environmental impact involved for which comments have not been requested specifically.

Comments concerning the proposed action and requests for additional information should be addressed to Forest Supervisor H. Reid Jackson, Forest Service Building, P.O. Box 1888, Jackson, Wyoming 83001. Comments must be received by November 2, 1976 in order to be considered in the preparation of the final environmental statement.

Dated: September 2, 1976.

Einar L. Roget, Associate Deputy Chief.

[FR Doc.76-26318 Filed 9-8-76; 8:45 am]

NOTICES

SOIL CONSERVATION SERVICE

WATKINS GLEN RESERVE CONSERVATION AND DEVELOPMENT (RC&D) MEASURE, N.Y.

Availability of Negative Declaration of Environmental Statement

Pursuant to Section 102(2) (C) of the National Environmental Policy Act of 1969; Part 1500.6(e) of the Council on Environmental Quality Guidelines (38 FR 20550), August 1, 1973; and Part 650.8(3) (3) of the Soil Conservation Service Guidelines (39 FR 19651), June 3, 1974; the Soil Conservation Service, U.S. Department of Agriculture, gives notice that an environmental impact statement is not being prepared for the Watkins Glen RC&D Measure, Schuyler County, New York.

The environmental assessment of this Federal action indicates that the measure will not create significant adverse local, regional, or national impacts on the environment and that no significant controversy is associated with the measure. As a result of these findings, Mr. Robert L. Hilliard, State Conservationist, Soil Conservation Service, USDA, U.S. Courthouse & Federal Building, 100 S. Clinton Street, Room 771, Syracuse, New York 13202, has determined that the preparation and review of an environmental impact statement is not needed for this measure.

The measure concerns a plan for flood prevention. The planned works of improvement include a floodwater diversion and the alteration of streets in the village of Watkins Glen.

The environmental assessment file is available for inspection during regular working hours at the following location: Soil Conservation Service, USDA, U.S. Courthouse & Federal Building, 100 S. Clinton Street, Room 771, Syracuse, New York 13202.

The negative declaration is available for single copy requests at the above location.

No administrative action on implementation of the proposal will be taken until September 24, 1976.

(Victor H. Barry, Jr., Deputy Administrator for Field Services, Soil Conservation Service.

August 30, 1976.

[FR Doc.76-26389 Filed 9-8-76; 8:45 am]

DEPARTMENT OF COMMERCE

Domestic and International Business Administration

BRIGHAM YOUNG UNIV.

Notice of Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to Section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89-651, 80 Stat. 887) and the regulations issued thereunder as amended (16 CFR 6(c)).

A copy of the record pertaining to this decision is available for public review during ordinary business hours of the Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76-00402. Applicant: Brigham Young University, Purchasing Department, Provo, Utah 84601. Article: Electron Microscope, Model EM 400 with an electronic goniometer stage (high tilt). Manufacturer: Philips Electronics Instruments, N.V., The Netherlands. Intended use of article: The article is intended to examine materials at low, intermediate and high magnifications, to investigate freeze-etch replicas at various magnifications, to examine thick specimens, to examine stereo pairs of various kinds of tissue with both freeze-etch and thin section preparations, for various applications of biochemistry at various magnifications, to examine thick specimens, and to apply analytical electron microscopy to various tissue systems in particular investigations. Specific projects include the following:

Elemental Analysis of Telosporus of Smut Fung.

Investigations of stereo pairs of biological materials.

Recombination of particles which constitute the photosynthetic apparatus.

Intracellular distribution of trace metals in higher plants.

Analysis of air particulates.

In addition, the article will be used for educational purposes in the following courses:

621 Electron Microscopy—To teach students principles of specimen preparation and handling and electron optics.

622 Electron Microscopy Laboratory—practical application of principles learned in 621.

526 Cell Biology—to teach principles of molecular physiology and ultrastructure of cells, and the effects of antibiotics upon eucaryotic organisms.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, from such purposes as this article is intended to be used, is being manufactured in the United States.

Reasons: The foreign article is equipped with an electronic goniometer stage which has a ±60 degree tilt. At the time the foreign article was ordered the most closely comparable domestic instrument was the Model EM 400 available from the Adam David Company, The Department of Health, Education, and Welfare (HEW) advised in its memorandum dated August 17, 1976 that the electronic goniometer stage of the article is pertinent to the applicant’s intended purposes. HEW further advises that the
EMU-4C does not have a scientifically equivalent enuculorulcenten stage. We, therefore, find that EMU-4C is not of equivalent scientific value to the foreign article for such purposes as this article is intended to be used.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for which this article is intended to be used, which is being manufactured in the United States.

(Std. 458.551; 80 Stat. 875). Interested persons may present their views with respect to the question of whether an instrument or apparatus of equivalent scientific value for the purposes for which the article is intended to be used is being manufactured in the United States. Such comments must be filed in triplicate with the Director, Special Import Programs Division, Office of Import Programs, Department of Commerce, Washington, D.C. 20230, within 20 calendar days after the date on which this notice of application is published in the Federal Register.

Amended regulations issued under cited Act (15 CFR 301) prescribe the requirements applicable to comments. A copy of each application is on file, and may be examined during ordinary Commerce Department business hours at the Special Import Programs Division, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76-00508. Applicant: DEB, National Institutes of Health, Laboratory of Biophysics, IRP, NINCDS, National Institute of Neurological Disease and Blindness, L-200, Woods Hole, MA 02545. Article: Ulromaticometer, Model LKB 8800A with Cryokit, Model 14800-1 and accessories. Manufacturer: LKB Produkter AB, Sweden. Intended use of article: The article is intended to be used for studies of the nervous system of several species of invertebrates and vertebrates. Special attention will be devoted to histological examination of diffuse substances within the cell after being taken up by the cell, and will be also investigated. Tracing specific synapses and other cell to cell contact with membrane specialization will be conducted after intracellular injection of markers to identified cells. Changes in intracellular spaces and in membrane structure or in membrane interaction between two neighboring cells induced by changes in their biochemical and biochemistry will be also studied. Application received by Commissioner of Customs: August 12, 1976.

Docket Number: 76-00509. Applicant: Virginia Commonwealth University, Department of Purchasing, Pullman, Washington 99102. Article: Combination PZ 8 Flasker and a FS 350 & Double Stream Mill (Ring Redner). Manufacturer: L. Fallman KG, West German. Intended use of article: The article is intended to be used in composition board research to prepare particles from various species of wood, types of raw material (chips, shavings, hog trim, sawdust, plywood trim). The objective of this research is to produce four times as much product from the same forest base now available. The article will also be used in NSE S50, Parameters for Synthesis of Wood Composition Materials, a course for graduates students covering the theory and practice of wood composite materials and developmental applications. Application received by Commissioner of Customs: August 16, 1976.

Docket Number: 76-00510. Applicant: Cornell University Medical College, 525 East 69th Street, New York New York 10021. Article: Blood Gas Electrode Meter Type D 22- modified for 110 V, 60 G current. Manufacturer: L. Escherich & Co., West Germany. Intended use of article: The article is a replaceable part for an existing blood gas instrument being used for investigation of oxygen and carbon dioxide tension in blood and cerebral spinal fluid. Application received by Commissioner of Customs: August 16, 1976.

Docket Number: 76-00511. Applicant: The University of Iowa, College of Medicine, Department of Physiology & Biophysics, Iowa City, Iowa 52240. Article: Flow scintillation counting system and accessories. Manufacturer: Berthold Instruments, West Germany. Intended use of article: The article is intended to be used for the study of peptide hormones and blood factors. Specifically, the article will be used for determination of the primary sequence of Somatomedins C isolated from human blood plasma which would allow synthesis of large quantities for treatment of patients having growth hormone deficiencies. Application received by Commissioner of Customs: August 16, 1976.

Docket Number: 76-00512. Applicant: Duke University, Department of Chemistry, Durham, North Carolina 27705. Article: Fourier Transformation Nuclear Magnetic Resonance Spectrometer System, Model JNM/FX-60. Manufacturer: JEOL Ltd., Japan. Intended use of article: The article is intended to be used for a broad range of research programs which involve the acquisition of nmr spectra of hydrogen, carbon-13, fluorine and phosphorus nuclei. The materials derived for this study will originate from research projects being conducted in the areas of inorganic, organic physical, analytical and biological chemistry. These research projects will include the following:

(a) Structural Studies of Alkaloids.
(b) Structural determinations of natural occurring diterpenoid alkaloids.
(c) Stereochmical assignments in alkaloids.
(d) Structural determinations of di-, sesq- and triterpenes.
(e) Structural studies on pharmaco- logically active constituents of marsh and beach plants of Georgia and the Southeast.
(f) Synthetic studies on complex alkaloids and terpenes.
(g) Identification and synthesis of chemically significant naturally occurring substances.
(h) Studies on bis-diterpenoid alkaloids.
(i) Studies on the biosynthesis of diterpene alkaloids.

The experiments to be performed with the article all involve pulse (Fourier transform) NMR spectroscopy on protons and carbon nuclei. In addition to recording spectra for determination of structure of natural products and synthetic intermediates, chemical shifts, and homo- and heteronuclear coupling constants, experiments will include the determination of positions and amounts of isotopic labelling (carbon 13), conformational free energies, and occasionally the quantitative analysis of mixtures for determination of optical purities. The educational purposes of the article involve the training of graduate students and postdoctoral associates in the use and applications of NMR spectroscopy to chemical problems under study. Application received by Commissioner of Customs: August 16, 1976.

Docket Number: 76-00514. Applicant: Duke University, Department of Chemistry, Durham, North Carolina 27705. Article: Fourier Transformation Nuclear Magnetic Resonance Spectrometer System, Model JNM/FX-60. Manufacturer: JEOL Ltd., Japan. Intended use of article: The article is intended to be used for a broad range of research programs which involve the acquisition of nmr spectra of hydrogen, carbon-13, fluorine and phosphorus nuclei. The materials derived for this study will originate from research projects being conducted in the areas of inorganic, organic physical, analytical and biological chemistry. These research projects will include the following:

(a) Structural Studies of Alkaloids.
NOTICES

Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76-09403. Applicant: Stanford University. Location of Meeting: Room S142, Stanford, California 94305. Article: Nikon Model M inverted microscope and accessories. Manufacturer: Nikon Optical Co., Japan. Intended Use of Article: The article is intended to be used for the study of the parasitic disease of man, schistosomiasis to obtain an understanding of the basic mechanisms of host-parasite interactions between the immature stages of the parasites and the fresh-water snails in which they develop. The article will also be used directly in the advanced training of postdoctoral fellows and other students.

Comments: No comments have been received with respect to this application.

Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States.

Reasons: The article provides an integrated system for cinephotomicrography. The Department of Health, Education, and Welfare (HEW) advises in its memorandum dated August 17, 1976, that the capability of the article described above is pertinent to the applicant's intended use. HEW also advises that it knows of no domestic instrument which provides the pertinent capability.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for purposes as this article is intended to be used, is being manufactured in the United States.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

RICHARD M. STEPPA,
Director,
Special Import Programs Division.

[FR Doc.76-26303 Filed 9-8-76; 8:45 am]

Economic Development Administration
LOCAL PUBLIC WORKS CAPITAL DEVELOPMENT AND INVESTMENT PROGRAM

Availability of Application Forms

Notice is hereby given that, pursuant to authority contained in section 107 of Title I of the Public Works Employment Act of 1976 (42 USC 6701 et seq.), application forms for assistance under the Local Public Works Capital Development and Investment Act of 1976 are now available.

The application forms may be obtained from the Economic Development Administration (EDA) Regional Offices. The following is a list of EDA Regional Offices.

Atlantic Regional Office, William J. Green, Jr., Federal Building, 600 Arch Street, Room 1824, Philadelphia, Pennsylvania 19106.
Southeastern Regional Office, 1300 Peachtree Street NE, Suite 700, Atlanta, Georgia 30309.

Midwestern Regional Office, 33 West Randolph Street, Room 1025, Chicago, Illinois 60601.

Southwestern Regional Office, 231 West Sixth Street, Suite 600, Austin, Texas 78701.

Rocky Mountain Regional Office, 900 17th Street, Suite 600, Denver, Colorado 80202.

Western Regional Office, 1700 Westlake Avenue, Suite 500, Seattle, Washington 98101.

No applications for financial assistance will be accepted until funds to implement the Local Public Works Capital Development and Investment Program have actually been appropriated and apportioned to and made available for use by EDA. EDA will publish notice in the Federal Register in advance of the date on which applications will be accepted.

Dated: September 1, 1976.

J. W. BEEN,
Assistant Secretary for Economic Development.

ELFSKIN CORP.

Petition for a Determination of Eligibility

A petition by Elfskin Corporation, Cherry Valley, Worcester, Massachusetts 01611, a producer of fabricatings and coated materials, was accepted for filing on September 2, 1976, under Section 331 of the Trade Act of 1974 (Pub. L. 93-181). Consequently, the United States Department of Commerce has initiated an investigation to determine whether an investigation to determine whether increased imports into the United States of articles like or directly competitive with those produced by the firm contributed importantly to total or partial separation of the firm's workers, or threat thereof, and to a decrease in sales or production of the petitioning firm.

Any party having a substantial interest in the proceedings may request a public hearing on the matter. A request for a hearing must be received on or before September 15, 1976.

Dated: September 2, 1976.

Jack W..Owen,
Chief, Trade Act Certification Division, Office of Planning and Program Support.

[FR Doc.76-26335 Filed 9-8-76; 8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Office of Education
ADVISORY COUNCIL ON FINANCIAL AID TO STUDENTS

Meeting

Notice is hereby given, pursuant to Section 10(a) (2) of the Federal Advisory Committee Act (P.L. 92-463), that the next meeting of the Advisory Council on Financial Aid to Students will be held on September 29 and 30, 1976, from 9:00 a.m. to 5:00 p.m. at the Hyatt Regency Hotel, Washington, D.C.

The Advisory Council on Financial Aid to Students is established under Section 476(a) of the Higher Education Act of 1965, as amended (20 U.S.C. 1093). The Committee shall advise the Commissioner on matters of general policy arising in the administration of the Commissioner's programs relating to financial assistance to students and on the evaluation of the effectiveness of these programs.

The meeting of the Committee shall be open to the public. The proposed agenda includes:

Assignment of work papers to be prepared by Council members on selected topics related to student financial aid. These papers will serve as basis for deliberation during the following meetings of the Council, preparatory to publishing its Third Annual Report to the Commissioner and to Congress.

Records shall be kept of all Committee Proceedings and shall be available for public inspection at the Council's Office located in Room 4931, Regional Office Building No. 3, 7th and D Streets, S.W., Washington, D.C. 20202.

Signed in Washington, D.C., on September 2, 1976.

Warren T. Troumman,
OS Delegate.

Office of the Secretary

ASSISTANT SECRETARY FOR ADMINISTRATION AND MANAGEMENT

Statement of Organization, Functions and Delegations of Authority

Part 1 of the Statement of Organization, Functions and Delegations of Authority of the Department of Health, Education, and Welfare, Office of the Secretary, Office of the Assistant Secretary for Administration and Management, is amended to revise Chapter 1730, Office of Administration (40 FR 11622), to combine into a single OS headquarters Equal Employment Opportunity Office the responsibilities for all OS headquarters equal employment opportunity programs. The revised Chapter reads as follows:

Section 1730.10 Organization. Delete: OS Equal Employment Opportunity Staff; OS Federal Women's Program Staff; OS Spanish-Speaking Program Staff.


Section 1730.20 Functions. Delete: G. OS Equal Employment Opportunity Staff; H. OS Federal Women's Program Staff; L. OS Spanish-Speaking Program Staff and substitute the following new section:

G. OS Office of Equal Employment Opportunity: Carries out equal employment opportunity activities within OS headquarters. Equal Employment Opportunity Office shall have a special focus minority groups and women as mandated by Executive Order 11478 and as amended by Pub. L. 92-261 42
NOTICES

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT
Office of Interstate Land Sales Registration
[Docket No. N-76-627]

SWANSBORO COUNTRY
Hearing


Pursuant to 15 U.S.C. 1701(d) and 24 CFR 1720.160(b).

Notice is hereby given that: 1. Swansboro Country, Richard H. Dyer, President, W & D Investment Company, authorized agent and officers, hereinafter referred to as “Respondent,” being subject to the provisions of the Interstate Land Sales Full Disclosure Act (Pub. L. 94-344) (15 U.S.C. 1701 et seq.) received a Notice of Proceedings and Opportunity for Hearing issued July 27, 1976, which was sent to the developer pursuant to 15 U.S.C. 1705(d), 24 CFR 1710.45 (b) (1) and 1720.125 informing the developer of information obtained by the Office of Interstate Land Sales Registration alleging that the Statement of Record and Property Report for Swansboro Country, located in El Dorado, County, California, contain untrue statements of material fact or omit to state material facts required to be stated therein or necessary to make the statements therein not misleading.


3. In said Answer the Respondent requested a hearing on the allegations contained in the Notice of Proceedings and Opportunity for Hearing.

4. Therefore, pursuant to the provisions of 15 U.S.C. 1705(d) and 24 CFR 1720.160(d), it is hereby ordered, That a public hearing for the purpose of taking evidence on the questions set forth in the Notice of Proceedings and Opportunity for Hearing be held before Judge James W. Mast, in Northern California, at a place to be determined, on October 6, 1976 at 10:00 a.m.

5. The following time and procedure is applicable to such hearing: All affidavits and a list of all witnesses are requested to be filed with the Hearing Clerk, HUD Building, Room 10150, Washington, D.C. 20410 not later than September 5, 1976.

6. The Respondent is hereby notified that failure to appear at the above scheduled hearing shall be deemed a default and the proceedings shall be determined against Respondent, the allegations of which shall be deemed to be true, and an order Suspending the Statement of Record, herein identified, shall be issued pursuant to 24 CFR 1710.45(b) (1).

This Notice shall be served upon the Respondent forthwith pursuant to 24 CFR 1720.440.

By the Secretary.

Dated: August 20, 1976.

JAMES W. MAST,
Administrative Law Judge.

[FR Doc.76-26357 Filed 9-8-76;8:45 am]

DEPARTMENT OF TRANSPORTATION
Federal Aviation Administration
AIR TRAFFIC PROCEDURES ADVISORY COMMITTEE
Meeting

Pursuant to section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 93-443; 5 U.S.C. App. D) notice is hereby given of a meeting of the Federal Aviation Administration Air Traffic Procedures Advisory Committee to be held October 12 through October 15, 1976, from 9 a.m. E.D.T. to 4 p.m. daily, except for the last day which will terminate at 1 p.m., in conference rooms 7A and B at FAA Headquarters, 800 Independence Ave., SW., Washington, D.C.

The agenda for this meeting is as follows: A continuation of the Committee's
NOTICES
Office of Hazardous Materials Operations
HAZARDOUS MATERIALS REGULATIONS-EXEMPTIONS

Notice of Grants and Denials of Applications for Exemptions
In accordance with the procedures governing the application for, and the processing of, exemptions from the Department of Transportation's Hazardous Materials Regulations (49 CFR Part 171), notice is hereby given of the exemptions granted July 1976. The names of the parties identified by a number in the "Nature of Exemption Granted" portion of the table below as follows: (1) Motor vehicle, (2) Rail freight, (3) Cargo vessel, (4) Cargo-only aircraft, (5) Passenger-carrying aircraft.

Application No.  Exemption No.  Applicant  Basis upon which exemption granted  Nature of exemption granted

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Exemption No.</th>
<th>Applicant</th>
<th>Basis upon which exemption granted</th>
<th>Nature of exemption granted</th>
</tr>
</thead>
<tbody>
<tr>
<td>4106-X</td>
<td>DOT-E 4106</td>
<td>Southern Oxygen Co.</td>
<td>To become a party to exemption No. 30 (see application No. 49 CFR Part 171)</td>
<td>49 CFR 173.33(a)</td>
</tr>
<tr>
<td>4105-Y</td>
<td>DOT-E 4105</td>
<td>American Cyanamid Co.</td>
<td>To become a party to exemption No. 30 (see application No. 49 CFR Part 171)</td>
<td>49 CFR 173.33(a)</td>
</tr>
<tr>
<td>4107-X</td>
<td>DOT-E 4107</td>
<td>Union Carbide Corp.</td>
<td>To become a party to exemption No. 30 (see application No. 49 CFR Part 171)</td>
<td>49 CFR 173.33(a)</td>
</tr>
</tbody>
</table>

Federal Aviation Administration

RADIO TECHNICAL COMMISSION FOR AERONAUTICS (RTCA) EXECUTIVE COMMITTEE

Meeting
Pursuant to section 10(a) (2) of the Federal Advisory Committee Act (Pub. L. 92-463; 5 U.S.C. App. 1) notice is hereby given of a meeting of the RTCA Executive Committee to be held September 24, 1976, RTCA Conference Room 261, 1717 H Street, N.W., Washington, D.C. 20006, commencing at 9:30 a.m. The agenda for this meeting is as follows: (1) Approval of Minutes of July 22-23, 1976 meeting; (2) Special Committee Activities Report for July-August 1976; (3) Chairman's Report of RTCA Administration and Activities; (4) Report of RTCA MOC/MPS Informal Review Group; (5) Consideration of establishing additional Special Committees.

Attendance is open to the interested public but limited to the space available. With the approval of the Chairman, members of the public may present oral statements at the hearing. Persons wishing to attend and persons wishing to present oral statements should notify, not later than the day before the meeting, and information may be obtained from Mr. Franklin L. Cunningham, Executive Director, Air Traffic Procedures Advisory Committee, Air Traffic Service, AAT-305, 800 Independence Ave., SW., Washington, D.C. 20591, telephone (202) 246-3728.

Any member of the public may present a written statement to the Committee at any time.

Issued in Washington, D.C., on August 22, 1976.

F. L. CUNNINGHAM,  
Executive Director, ATPAC.

[FEDERAL REGISTER Vol. 41, No. 176—Thursday, September 9, 1976]
## Notices

### Request

**725-P-DOT-E 7825**
- **Applicant**: Air Products & Chemicals, Allentown, Pa.
- **Nature of exemption thereafter**: To become a party to exemption 7825.

**726-X-**
- **Applicant**: Federal Express Corp., Knoxville, Tenn.
- **Regulation(s) affected**: 49 CFR 300.24.
- **Nature of exemption thereafter**: To become a party to exemption 7800.

**723-X-**
- **Applicant**: TMT Trailer Ferry, Inc., Jacksonville, Fla.
- **Nature of exemption thereafter**: To waive certain operational requirements pertaining to motor vehicles containing inflammable liquids and require a minimum aggregate load.

**725-**
- **Applicant**: Structural Composite Industries, Inc., Arcata, Calif.
- **Regulation(s) affected**: 49 CFR 173.320(c)(1).
- **Nature of exemption thereafter**: To authorize shipment of compressed air in non-DOT specification filament-wound reinforced plastic (FRP) aluminum lined cylinders. (Modes 1, 2, 3, 4, and 5.)

**727-**
- **Applicant**: Shipley Co., Inc., Newton, Mass.
- **Nature of exemption thereafter**: To ship cast iron, liquid in a DOT specification 78 portable tank.

**728-**
- **Applicant**: Virginia Chemical Co., Richmond, Va.
- **Regulation(s) affected**: 49 CFR 173.5(a).
- **Nature of exemption thereafter**: To ship flammable corrosive liquids in non-DOT specification MC-200 cargo tank. (Mode 1.)

**729-**
- **Applicant**: Aerojet Solid Propulsion Co., Sacramento, Calif.
- **Regulation(s) affected**: 49 CFR 173.50-200.
- **Nature of exemption thereafter**: To authorize commercial shipment of rocket motors, class D, explosives in non-DOT specification plywood boxes. (Mode 2.)

**732-**
- **Applicant**: United States Steel Corp., McKeeseport, Pa.
- **Nature of exemption thereafter**: To ship certain flammable and nonflammable compressed gases in 3 non-DOT specification seamless wire hoop-wrapped steel cylinders, complying with DOT specifications.

**733-**
- **Applicant**: Hooker Chemicals & Plastics Corp., Niagara Falls, N.Y.
- **Regulation(s) affected**: 49 CFR 173.50-10.
- **Nature of exemption thereafter**: To ship ferrophosphorus in non-DOT specification steel drums loaded in containers. (Mode 2.)

**734-**
- **Applicant**: The Carborundum Co., Newark, N.J.
- **Nature of exemption thereafter**: To ship waste corrosive liquids, n.o.s., in a non-DOT specification tank car, as defined in 49 CFR 173.120. (Mode 3.)

**735-**
- **Nature of exemption thereafter**: To ship certain flammable cryogenic liquids in a non-DOT specification cargo tank. (Mode 3.)

**736-**
- **Nature of exemption thereafter**: To ship methyl ethyl ketone and toluol in a DOT specification 27 portable tank. (Mode 1.)

**737-**
- **Applicant**: Gulf Insurance Co., Baton Rouge, La.
- **Nature of exemption thereafter**: To ship hydrogen chloride, anhydrous in a non-DOT specification cargo tank. (Mode 3.)

### Emergency Exemption

**EE7838-X DOT-E 7827**
- **Applicant**: TMT Trailer Ferry, Inc., Jacksonville, Fla.
- **Nature of exemption thereafter**: To transport motor vehicles containing fuel of certain types with certain operational requirements waived. (Mode 2.)

### Denials

**70-112**
- **Request by**: American Hoechst Corp., Somerville, N.J.
- **Nature of exemption**: To ship various hazardous materials in containers complying with DOT Specification 37A except for markings.

**70-509**
- **Request by**: BASF Wyandotte Corp., Parsippany, N.J.

**70-372**
- **Nature of exemption**: To ship a 52 percent concentration of carbon tetrachloride in a DOT Specification 210 fiber drums, described as "Drugs, Chemicals, Medical or Cosmetics, n.o.s., Solid," denied July 28, 1976.

**70-387**
- **Request by**: Beech Aircraft Corp., Wichita, Kan.
- **Nature of exemption**: To transport nonspillable aircraft batteries in excess of fifty pounds in an inaccessible cargo pit of any aircraft.

**70-398**
- **Request by**: Mobil Chemical Company, Richmond, Va.
- **Nature of exemption**: To amend U.S. Coast Guard SP 43-71 to allow carriage of phosphorus' oxychloride in specially designed portable tanks, denied July 7, 1976.

**70-750**
- **Request by**: Boeing Aircraft Corp., Seattle, Wash.
- **Nature of exemption**: To ship 2100 authorized shipping of toluene, a flammable liquid, in a DOT Specification 210 fiber drums, denied June 26, 1976.

**70-14**
- **Request by**: Trans-World Airlines, Inc., Kansas City, Mo.
- **Nature of exemption**: To ship 2100 authorized shipping of toluene, a flammable liquid, in a DOT Specification 210 fiber drums, denied June 15, 1976.

**70-603**
- **Request by**: Teller Instruments Corp., Tarrytown, N.Y.
- **Nature of exemption**: To ship caustic soda, liquid in a DOT specification 37 portable tank.

**70-282**
- **Request by**: DOT-E 724.
- **Nature of exemption**: To ship cyprinohexoide in foreign-made drums containing 50 pounds of fish. (Mode 3.)

**70-371**
- **Request by**: DOT-E 72.
- **Nature of exemption**: To ship cast iron, liquid in a DOT specification 78 portable tank.

**76-75**
- **Request by**: DOT-E 703.
- **Nature of exemption**: To ship caustic soda, liquid in a DOT specification 37 portable tank.

### Office of Pipeline Safety Operations

**Docket No. 76-10**

**TRANS-ALASKA CRUDE OIL PIPELINE**

**Grant of Waiver**

By letter dated March 19, 1976, the Alyeska Pipeline Service Company (Alyeska) requested a waiver from compliance with the welding requirement of 49 CFR 193.218 with respect to girth weld No. 493447 at the completed Jim River Crossing No. 2 on the Trans-Alaska crude oil pipeline. This girth weld serves to tie-in two sections of double coated pipe in the 620-foot crossing. Section 193.218 requires that longitudinal weld seams on adjacent length of pipe must be offset. However, at weld No. 493447, the seam on adjacent pipe lengths are abutting, not "offset" as required.

In requesting the waiver, Alyeska asserted that "there are no metallurgical or safety reasons for offsetting longitudinal seams on liquid pipelines." As further support for the waiver, Alyeska submitted that at the factory in Japan each seam had been ultrasonically inspected over its entire length and radiographed for a distance of eight inches from each end. Also, Alyeska said the girth weld was radiographically tested in the field and found acceptable under the standards of API Standard 1104 (1973 ed.), which are incorporated by reference in 49 CFR 195.238. Alyeska further stated that the entire crossing was hydraulically tested to at least 1152 psi, or 82 percent of specified minimum yield strength (SMYS), and that the operating pressure at the weld is not exceed 760 psi, or 60 percent of SMYS. (To meet the requirements of 49 CFR 195.302, the crossing must be tested again for 24 hours before being placed in operation.)

After reviewing the information and arguments presented by Alyeska, the Office of Pipeline Safety Operations (OPSO) denied the waiver request by letter dated August 6, 1976. The request was denied because Alyeska did not convincingly demonstrate that offsetting of seams is not necessary for safety at weld No. 493447. OPSO stated that even though the previous test data indicate an absence of unacceptable defects, "the data do not demonstrate that the concentration of stresses at the intersection of welds would not eventually indicate an absence of unacceptable stress concentration at the intersection of welds."

### Reference

**EE7488-X Request by Mr. Michael Goldhammer, Portland, Ore.—For an emergency exemption to carry as carry-on baggage, his battery-powered wheelchair, a passenger-carrying aircraft, denied July 10, 1976.**

**Office of Pipeline Safety Operations**

**FEDERAL REGISTER Vol. 41, No. 176—Thursday, September 9, 1976**
why compliance with Section 195.218 would not be in the public interest.

On August 12, 1976, Alyeska submitted a petition for reconsideration. In their petition, Alyeska argues that because of the excellent notch toughness properties of the pipe and girth weld materials at weld No. 49344T, even the presence of surface flaws would not be a problem at the intersection of welds and thus a fracture would not result from the cyclic loading to which the pipe and girth weld materials with similar tensile and notch toughness properties between material properties of the girth weld and pipe metal minimizes the likelihood of any concentration of residual stresses caused by excess metal at the intersection of welds. (The longitudinal seams were ground flush with the inside circumference at pipe ends. The longitudinal seams were ground flush with the inside circumference at the intersection of welds. (The longitudinal seams were ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone. 4. The fact that the longitudinal seams are ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone.

On August 13, 1976, OPSO asked Alyeska to supplement its petition with data on the mechanical properties of the girth weld and pipe materials. The requested data indicates that the mechanical properties of elongation, hardness, and fracture toughness (as evidenced by high Charpy V-Notch energy levels at low temperatures) greatly exceed the pipeline's specifications for sound ductile welds. The data further indicates that the pipe and girth weld materials have similar tensile and notch toughness properties.

Additionally, OPSO discussed the welding problem with welding engineering experts outside the Government. In the opinion of these experts, the strength of the weld would not be reduced by the abutting longitudinal seams. The experts also agreed that the weld at its underwater location could reduce the pipeline's integrity, particularly in view of the apparently high quality of the existing weld. The latter opinion is premised by the many difficulties associated with properly replacing an existing girth weld under adverse working conditions.

Finally, OPSO asked the Department's welding/radiographic experts in Alaska to examine the radiograph of weld No. 49344T to determine the condition of the weld. The experts reported that the weld is of very high quality and exceeds the standards of acceptability under Sec. 6 of API Standard 1104 as incorporated by reference in 49 CFR 195.225.

The Materials Transportation Bureau (MTB) has reviewed the additional information and arguments submitted by Alyeska in connection with its petition for reconsideration. In its petition and other relevant considerations, MTB finds that the requested waiver is not inconsistent with pipeline safety and is in the public interest. The reasons for this decision are as follows:

1. The girth weld exceeds the standards of acceptability in Sec. 6 of API Standard 1104 and does not contain any weld defect which might grow to an unacceptable degree. (The longitudinal seams were ground flush with the inside circumference at the intersection of welds. (The longitudinal seams were ground flush with the inside circumference at the intersection of welds and surrounding heat-affected zone.

2. The ductility of the pipe and girth weld metals would provide for localized yielding where high residual stresses may exist and thereby prevent fracture initiation and failure of the weld. (Section 195.218 was adopted when pipe and weld materials in general use were less ductile than the materials at weld No. 49344T.)

3. The similarity of mechanical properties between the girth weld and pipe metals minimizes the likelihood of any concentration of residual stresses caused by excess metal at the intersection of welds. (The longitudinal seams were ground flush with the inside circumference at pipe ends when the pipe was manufactured to accommodate an internal line-up clamp during welding.)

4. Replacing weld No. 49344T to comply with Section 195.218 could reduce the pipeline's integrity because of the difficulties in cutting out a segment of the concrete coated cross section, rotating and realigning it, especially in view of the adversities of working in a 30-foot excavation in a river crossing. Accordingly, effective immediately, Alyeska is hereby granted a waiver from compliance with 49 CFR 195.218 with respect to weld No. 49344T at the Jim River Crossing No. 2 on the Trans-Alaska crude oil pipeline.

Issued in Washington, D.C. on September 17, 1976.

JAMES T. CURRIS, JR.,
Registrar,
Materials Transportation Bureau.

C. H. WATERMAN INDUSTRIES

Petition for Temporary Exemption From Federal Motor Vehicle Safety Standard

C. H. Waterman Industries of Athol, Massachusetts, has petitioned for a 2-year exemption from 57.1.1 of Motor Vehicle Safety Standard 208, for an electric powered passenger car on grounds that it would facilitate the development and field evaluation of a low-emission motor vehicle.

Waterman has previously been granted an exemption expiring May 1, 1977, from all or a portion of 15 Federal motor vehicle safety standards, for a European passenger car that it converts to electric propulsion. (49 FR 23125) The company has imported seven such vehicles for tests, and none have been sold for public use. Waterman's current petition states that it has experienced difficulty in converting systems that incorporate "automatic and/or emergency locking and adjusting features", which, it says, must be designed in conjunction with the design of the vehicle structure in order to integrate the two in a practicable manner. Waterman has not found it possible to date to install in its automobile a restraint system of the sort required by Standard No. 208 since January 1972.

The company argues that the exemption will not unreasonably degrade the safety of the vehicle as it will be equipped with non-retractable Type 2 belt systems in the front seats, and Type 1 lap belts in the rear offering protection equivalent to conforming systems. Waterman argues that it is in the public interest to develop its alternative to the internal combustion engine "despite the small inconveniences of a manually adjusted restraint system."

This notice of receipt of a petition for temporary exemption is published in accordance with the NHTSA regulations on this subject (49 CFR 555.1), and does not represent any agency decision or other exercise of judgment concerning the merits of the petition.

Interested persons are invited to submit comments on the petition of C. H. Waterman Industries, described above. Comments should refer to the docket number and be submitted to: Docket Section, National Highway Traffic Safety Administration, Room 1108, 400 Seventh Street, SW., Washington, D.C. 20590. It is requested but not required that 10 copies be submitted.

All comments received before the close of business on the comment closing date indicated below will be considered. The application and supporting materials and all comments received after the closing date will also be filed and considered to the extent possible. If the petition is granted, notice will be published in the Federal Register pursuant to the authority indicated below.

Comment closing date: October 12, 1976.

Proposed effective date: Date of issuance of exemption.

ROBERT L. CASEY,
Associate Administrator,
Motor Vehicle Programs.

CIVIL AERONAUTICS BOARD
AIR NEW ENGLAND, INC.

Meeting

Notice is hereby given that a presentation will be made by Air New England.
Inc., on Thursday, September 23, 1976, at 10:00 a.m. (local time), in Room 1027, Universal Building, 255 Connecticut Avenue, N.W., Washington, D.C., regarding the status of the carrier as a result of the recent change in its management.


PHYLLIS T. KAYLOR, Secretary.

[FR Doc.76-26334 Filed 9-3-76;8:45 am]

THE FLYING TIGER LINE INC.

Meeting

Notice is hereby given that a presentation will be made by The Flying Tiger Line Inc., on Wednesday, September 27, 1976, at 10:00 a.m. (local time), in Room 1027, Universal Building, 255 Connecticut Avenue, N.W., Washington, D.C., regarding the marketing study made by the carrier.


PHYLLIS T. KAYLOR, Secretary.

[FR Doc.76-26345 Filed 9-8-76;8:45 am]

[Docket 27618; Agreement G.A.B. 26906 R-1 through R-15; Order 76-9-147]

INTERNATIONAL AIR TRANSPORT ASSOCIATION

North/Central Pacific Passenger Fares

Issued under delegated authority August 27, 1976.1

An agreement has been filed with the Board pursuant to section 412(a) of the Federal Aviation Act of 1958 (the Act) and Part 261 of the Board's Economic Regulations between various air carriers, foreign air carriers, and other carriers embodied in the resolutions of the Traffic Conferences of the International Air Transport Association (IATA). The agreement, establishing North/Central Pacific fares from October 1, 1976 through March 31, 1977, was adopted at a conference held in New York on June 3-4, 1976.

As set forth in the attached appendices, Tokyo-Honolulu/west coast fares would take increases ranging from 3 to 19 percent. Normal economy fares would increase 3 percent and first-class and most promotional fares would increase 5 percent. However, the affinity group fare for 100 or more persons, available only for U.S. originations, would increase by 10 percent and the basic season group tour (GTT) fare would increase by 14 to 19 percent. Fares to other Far Eastern destinations would, in general, remain at present levels except that first-class fares would increase 4 percent and the basic season GTT fare would increase up to 7 percent.

Most fares from Anchorage would also remain at present levels except first-class, basic season GTT, and affinity group 100 fares to Japan which would increase 4, 7 and 10 percent, respectively.

1Appendices filed as part of the original document.

Two new 30/120-day excursion fare plans are proposed: one for round-trip travel eastbound from several Asian points to the Western Hemisphere, and a second for round-trip travel westbound from Canada to similar Asian destinations but at lower levels than those proposed for eastbound travel.

Lastly, the agreement would remove stopover restrictions on use of GTT fares and would permit passengers using this fare to return individually from their last point of embarkation in Asia to their point of origin in the Western Hemisphere.2

The purpose of this order is to establish procedural dates for the submission of carrier justification-in support of the agreement and comments from interested persons. The carriers' justifications should be set out in the tabular format suggested in Order 76-8-147, July 17, 1976, with historical data as reported to the Board in Form 41 reports by functional account for total transpacific services for the 12 month period ended June 30, 1976, adjusted to exclude market areas not covered by the agreement, e.g. South Pacific, and thus entitled cargo and charter operations pertaining to the North/Central Pacific market as to establish the present economic status of scheduled passenger services in the North/Central Pacific market area covered by the agreement. The carriers will also be expected to include a forecast for the period ending September 30, 1977, both including and excluding the increased fares for which approval is sought. The carriers are required to allocate costs between the passenger and cargo components of scheduled passenger aircraft by the "space method" stipulated by the Board in its April 2, 1970 decision in Docket 18381, Nonpriority Mail Rates, Orders 70-4-9 and 70-4-10.3 In addition, the carriers are required to submit detailed traffic data showing revenue passenger miles and revenue by specific fare categories as well as load factor information both for the historical period and for the forecast period and including and excluding the increased fares for which approval is sought.

Northwest Airlines, Inc., a non-IATA carrier, will be required to file data similar to that required of the IATA carriers so that a full economic picture of U.S. carrier-operations in the area under consideration may be obtained in order that the Board may be in a position to make a meaningful evaluation in its disposition of the agreement.

Accordingly, IT IS ORDERED THAT:

1. All United States air carrier members of the International Air Transport Association providing North/Central Pacific combination service shall file, within 15 calendar days after the date

2. Northwest Airlines, Inc. shall file within 15 calendar days after the date of service of this order, data similar to that required of the IATA carriers.

3. Comments and objections from interested persons and parties shall be submitted within 15 calendar days after the date of service of this order;

4. Replies to submissions received in response to ordering paragraphs 1 and 2 above and replies to comments received pursuant to ordering paragraph 3 above shall be submitted within 25 calendar days after the date of service of this order; and

5. Insofar as air transportation as defined by the Act is concerned, tariffs implementing the subject agreement shall not be filed in advance of Board action on the subject agreement.

This order will be published in the Federal Register.

By James L. Deegan, Chief, Passenger and Cargo Rates Division, Bureau of Economics.

PHYLLIS T. KAYLOR, Secretary.

[FR Doc.76-26347 Filed 9-8-76;8:45 am]

[Docket 51162]

OHIO/INDIANA POINTS NONSTOP SERVICE INVESTIGATION

Notice of Postponement and Rescheduling of Hearing

Notice is hereby given, pursuant to the provisions of the Federal Aviation Act of 1958, as amended, that the hearing in the above-entitled proceeding presently scheduled to be held on September 30, 1976 (41 F.R. 36537, August 30, 1976) in Columbus, Ohio and then to reconvene on October 5, 1976 in Washington, D.C., is hereby postponed to October 13, 1976 at 10:00 a.m. (local time) in Room 1003, Hearing Room A, Universal Building North, 1565 Connecticut Avenue N.W., Washington, D.C. The entire hearing will be held at the above time and place in Washington, D.C., and the Columbus, Ohio portion of the hearing is hereby cancelled.

Dated at Washington, D.C., September 2, 1976.

WILLIAM H. DAPPLE, Administrative Law Judge.

[FR Doc.76-26346 Filed 9-8-76;8:45 am]

COMMITTEE FOR THE IMPLEMENTATION OF TEXTILE AGREEMENTS

ESTABLISHMENT OF EXPORT VISA REQUIREMENT AND CERTIFICATION FOR EXEMPT TEXTILE PRODUCTS FROM THE REPUBLIC OF THE PHILIPPINES

August 31, 1976.

Under the terms of the Bilateral Cotton, Wool and Man-Made Fiber Textile Agreements, each carrier should provide complete explanatory supporting detail including statistical data to describe the methods used in making the allocations.
Agreement of October 15, 1975, between the Governments of the United States and the Republic of the Philippines. The Government of the Philippines has undertaken to limit its exports of cotton, wool and man-made fiber textile products to the United States to the percentage levels stated in the letter set forth below. Pursuant to this agreement, the Governments of the United States and the Republic of the Philippines have established an administrative mechanism to preclude circumvention of the system of restraint established for exports to the United States of cotton, wool and man-made fiber textile products, produced or manufactured in the Republic of the Philippines. The two governments have also agreed to establish an administrative mechanism to exempt from the levels of restraint of the bilateral agreement: (1) shipments of cotton, wool and man-made fiber textile products valued under $250; (2) hand-made cottage industry products of handloomed fabrics; and (3) traditional Philippine folklore handicraft textile products.

Effective on October 10, 1976, entry into the United States for consumption and withdrawal from warehouse for consumption of any cotton, wool or man-made fiber textile products, produced or manufactured in the Republic of the Philippines and exported on or after that date for which the Government of the Republic of the Philippines has not issued an appropriate export visa or certification for exemption, will be prohibited. Application of these requirements to cotton, wool and man-made fiber textile products exported prior to October 10, 1976, is to become effective on December 3, 1976.

The export visa will be a circular stamp in blue ink on the front of the invoice (Special Customs Invoice Form 5515, successor document, or commercial invoice when such form is used) and will include the signature and title of an official authorized by the Government of the Philippines to issue visas.

Cotton, wool and man-made fiber textile products that are to be exempted from the levels of restraint of the bilateral agreement shall be accompanied by a copy of the invoice issued by the Government of the Republic of the Philippines.

The certification will be a rectangular stamp in blue ink on the invoice (Special Customs Invoice Form 5515, successor document, or commercial invoice when such form is used) and will include the signature and title of an official authorized by the Government of the Republic of the Philippines to issue the certificate; identify the items exempted; indicate the date the certification was signed and certified; and carry the certificate number. In the space marked "Description" on the certification stamp, the Government of the Republic of the Philippines will indicate that the shipment is either valued at less than $250; has an exempt certification but is either valued at less than $250; is a hand-made cottage industry product of handloomed fabrics; or will include the name of the particular Philippine folklore product. A copy of the certification stamp is also enclosed.

An export visa will not be required to accompany shipments of exempt cotton, wool and man-made fiber textile products.

Cotton, wool and man-made fiber textile products exported from the Republic of the Philippines prior to the effective date of this directive shall not be denied entry until December 9, 1976. Merchandise covered by an invoice without an export visa, or an export visa which includes both exempt and non-exempt textile products, will be denied entry.

You are directed to permit entry into the United States for consumption and withdrawal from warehouse for consumption of designated shipments of cotton, wool, and/or man-made fiber textile products, produced or manufactured in the Republic of the Philippines, notwithstanding the designated shipment or shipments do not fulfill the aforementioned visa and certification requirements. An exempt certification shall not be required by the Committee for the Implementation of Textile Agreements.
CONSUMER PRODUCT SAFETY COMMISSION

TECHNICAL ADVISORY COMMITTEE ON POISON PREVENTION PACKAGING

NOTICE OF MEETING

Notice is given that the Technical Advisory Committee on Poison Prevention Packaging will meet on September 28, 1976 (8:30 a.m. to 5:00 p.m.) and September 29, 1976 (9:00 a.m. to 4:00 p.m.) at the Consumer Product Safety Commission, 750 K Street, N.W., 6th Floor Conference Room.

The purpose of the Technical Advisory Committee is to provide advice and recommendations on the types and kinds of packaging that will protect children from injury or illness resulting from handling or ingestion of household substances.

The agenda for the Tuesday, September 28, meeting will include orientation for new members during the morning session and a discussion of concepts of child-resistant packaging by the full Committee during the afternoon session. On Wednesday, September 29, the morning session will be devoted to (1) a report on the Administrator’s Proposal, (2) draft proposal to regulate household cleaning and maintenance products containing petroleum distillates, and (3) requests for exemption outstanding. A discussion on compliance activities under the Poison Prevention Packaging Act will take place in the afternoon.

Persons wishing to make oral or written presentations to the Committee should notify the Secretary of the Consumer Product Safety Commission at least five days in advance of the meeting. The meeting is open to the public, however, space is limited. Further information concerning this meeting may be obtained from the Office of the Secretary, Consumer Product Safety Commission, Washington, D.C. 20207, phone (202) 634-7700.

Dated: September 2, 1976.

SAVYE E. DUNN,
Secretary, Consumer Product Safety Commission.

ENVIRONMENTAL PROTECTION AGENCY

[OPP-00526; FR 41:6] CHLORODANE AND HEPTACHLOR

Notice of Availability of Draft Environmental Impact Statement

On May 7, 1974, the Environmental Protection Agency (EPA) published in the Federal Register (39 FR 16168) a statement of policy announcing its intention to prepare Environmental Impact Statements in accordance with section 102(2)(C) of the National Environmental Policy Act of 1969, in connection with its most significant regulatory actions, although not required to do so by law.

Pursuant to that policy announcement, the EPA has prepared a Draft Environmental Impact Statement (EIS) on the proposed cancellation of chlordane and heptachlor. On November 18, 1974, the Administrator of the EPA determined that the continued registration and use of pesticides containing chlordane or heptachlor posed a substantial question of safety, and accordingly a Notice of Intent to cancel was issued; this Notice was published in the Federal Register (39 FR 41206). However, subsequent to the issuance of the Notice, new evidence came to the attention of the Administrator which confirmed and heightened the human cancer hazard posed by these pesticides. As a result, on July 28, 1975, the Administrator announced his intention to suspend the registration of pesticide products containing chlordane and heptachlor for all uses for which cancellation had been proposed in the Federal Register Notice mentioned, pending a final cancellation decision. This Notice of Intent to suspend was issued in accordance with the “imminent hazard” provisions under sections 6(c) and 21(f) of the amended Federal Insecticide, Fungicide, and Rodenticide Act (F.I.R.A. C. 136), and was published in the Federal Register on August 15, 1975 (40 FR 34456). On December 24, 1975, following 45 days of public hearings, the Administrator issued a decision and order on June 2, 1976, suspending the registration of all products containing chlordane, except in a minor, corn-borer control use, and heptachlor.

The EIS, a document totalling 51 pages including appendices, summarizes scientific information on chlordane and heptachlor with regard to toxicity to humans and animals, hazards to the environment, and costs and benefits of cancellation and other alternative regulatory actions. Significant facts about chlordane and heptachlor are:

1. They have been used for over 20 years in considerable quantities for a variety of crop and noncrop pest control purposes.
2. They are chemically similar; chlordane contains about 10% heptachlor.
3. They and their toxic breakdown products are very persistent in the environment, resisting chemical or biological breakdown into harmless substances.
4. They or their toxic breakdown products are found as residues throughout the environment, i.e., in soil, water, air, wildlife, and food.
5. Their toxic breakdown products are found to have accumulated in human adipose tissue and in human milk.
6. They and some of their breakdown products are acutely toxic to many forms of life, in addition to target species.
7. Heptachlor epoxide has been found to have accumulated in the organs of stillborn infants.
8. Heptachlor, heptachlor epoxide and chlordane induce tumors in laboratory animals, and thus pose a cancer threat to man.
9. If cancellation occurs, economic impact on agricultural commodities and consumer prices would be minor, com-
pared with normal year-to-year variations due to weather and other market factors.

EPA will file a copy of this draft statement with the Council on Environmental Quality on September 12, 1976. All comments on the EIS must be received by EPA within 45 days after the Council on Environmental Quality also lists its availability in the Federal Register. To be sure of receiving full consideration on the preparation of the final EIS, all comments should reach EPA within this time frame, and should bear the identifying notation OPP-00032. Comments should be filed in triplicate and addressed to EPA, Office of the Federal Register Section, Attn: Sandy Radinsky, Technical Services Division (WEF-569), Office of Pesticide Programs, Room 401, East Tower, 401 M Street, SW., Washington, D.C. 20460.

Two background reports on chlordane and heptachlor are available along with a copy of this draft statement. One report, "Pesticidal Aspects of Chlordane and Heptachlor in Relation to Man and Environment; A Further Review, 1972-1976"(855 pages), presents the economic and social implications of regulatory actions and EPA economic testimony at the chlordane/heptachlor suspension hearings.

Copies of the EIS and accompanying background materials have been forwarded to Federal agencies, state pesticide groups, EPA regional offices, national environmental and conservation organizations and agricultural, trade and chemical groups.

This EIS and background materials are available for inspection in the EPA Office of the Federal Register Section (see address above); single copies of these materials will be provided free of charge.


ANDREW W. BREIDENBACH,
Assistant Administrator for Water and Hazardous Materials.

[FR Doc.76-26409 Filed 9-8-76; 8:45 am]

[FRL 613-7]

ENERGY RELATED AUTHORITY

Report on Progress and Impact

Section 119(c)(2) of the Clean Air Act, as amended by the Energy Supply and Environmental Coordination Act of 1974, directs the Administrator to publish in the Federal Register at no less than 180 day intervals beginning January 1975, certain reports and findings on the implementation of EPA's energy related authority under section 119 of the Act. Specifically, the Administrator is directed to publish a concise summary of progress reports required to be filed by any person or source owner or operator to September 12, 1976. These extensions provisions of subsection 119(c) apply. Such reports are to include information on the status of compliance with requirements imposed by the Administrator under subsection 119(c). In addition, the Administrator is directed to publish up-to-date findings on the implementation of State Implementation Plans and upon ambient air quality. On January 27, 1976, and February 23, 1976, notices of subsection 119(c)(2) were published in the Federal Register at 40 FR 4034, 40 FR 33469 and 41 FR 7869 respectively.

As of July 15, 1976, some applications for compliance date extensions under subsection 119(c) have been received by the Administrator; however, no such extensions have been granted as yet. Therefore, no progress reports were required of or filed by any person or source owner or operator under subsection 119(c). In addition, no postponements under subsection 119(c) were sought or granted before July 15, 1976. No actions taken during the period covered by this report resulted in any impact on air quality or state implementation plans.

Whenever the Administrator issues an order to a fuel-burning source under section 2(a) of the Energy Supply and Environmental Coordination Act of 1974, after July 30, 1975, the Administrator of EPA is required to notify FEA if the source can burn coal and comply immediately with all applicable air pollution requirements without a compliance date extension. If such notification is not given, then the EPA Administrator must certify to FEA: (1) when the source can comply with standard conditions and/or regional limitations in the case of a source which is receiving a compliance date extension; or (2) when the source can comply with all air pollution requirements without a compliance date extension. If such notification is not given, then the EPA Administrator must certify to FEA: (1) when the source can comply with standard conditions and/or regional limitations in the case of a source which is receiving a compliance date extension; or (2) when the source can comply with all air pollution requirements without a compliance date extension.

As of July 15, 1976, the Administrator of EPA has notified FEA that seven plants can burn coal and comply immediately with all air pollution requirements without a compliance date extension. Those plants are: (1) Ames Station, Unit 1, Ames Electric Utility, Ames, Iowa; (2) Marshall Steam Station, Unit 14, Iowa Public Service Company, Waterloo, Iowa; (3) Des Moines Station, Units 10 and 11, Iowa Power and Light Company, Des Moines, Iowa; (4) Weston Station, Unit 2, Wisconsin Public Service Corporation, Rothschild, Wisconsin; (5) McWilliams Station, Unit 3, Alabama Electric Cooperative Inc., Guntersville, Alabama; (6) Nebraksa Public Power District, Columbus, Nebraska; and (7) Kipling 3 Station, Units 1 and 2, Kansas City Board of Public Utility Commissioners.

Also, the Administrator of EPA has certified to FEA that the following six stations cannot comply with all applicable air pollution requirements until the standards are determined for compliance, and therefore cannot receive compliance date extensions: (1) St. Clair Station, Unit 5, Detroit Edison Company, East China, Michigan; (2) Edge Moor Station, Units 1, 2, 3, 4, and 5, Delaware Power and Light Company, Wilmington, Delaware; (3) Crane Station, Units 1 and 2, Baltimore Gas and Electric Company, Baltimore, Maryland; (4) Wagner Station, Units 1 and 2, Baltimore Gas and Electric Company, Baltimore, Maryland; (5) Rockville Station, Units 4 and 5, Baltimore Gas and Electric Company, Baltimore, Maryland; and (6) Winnetka Station, Units 5, 6, 7, and 8, Village of Winnetka, Winnetka, Illinois.

FEDA's orders for these plants, therefore, cannot become effective until after January 1, 1979.

Two units at one plant (Hawthorne Station, Units 4 and 5, Kansas City Power and Light Company, Kansas City, Missouri) were ineligible for compliance date extensions because the units had generated more than half of their electricity through the use of coal during the period between Sept. 15, 1973 and March 15, 1974. The Administrator therefore certified January 1, 1977 and December 15, 1978 as the earliest dates on which the Federal Energy Administration's prohibition orders to units 4 and 5, respectively, may take effect. The Administrator also certified to FEA that the following two power plants will be able to burn coal in compliance with all applicable air pollution requirements within 6 months of the issuance of FEA's Notice of Effective Necessity to the plants: (1) Chesterfield Station, Units 3, 4, 5, and 6, Virginia Electric Power Company, Chester, Virginia; and (2) Morgantown Station, Units 1 and 2, Potomac Electric Power Company, Newburg, Maryland.

Dated: August 31, 1976.

STANLEY W. LEROY,
Assistant Administrator for Enforcement.

[FR Doc.76-26402 Filed 9-8-76; 8:45 am]

[OPP-180003; FRL 613-5]

MASSACHUSETTS DEPARTMENT OF ENVIRONMENTAL QUALITY ENGINEERING

Issuance of a Specific Exemption To Use Guthion To Control the Carrot Weevil

Pursuant to the provisions of section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (66 Stat. 973; 7 U.S.C. 136), notice is hereby given that the Environmental Protection Agency (EPA) has granted a specific exemption to the Massachusetts Department of Environmental Quality Engineering thereafter referred to as the Applicant). Asimina thompsoni (Guthion to Control the Carrot Weevil in Middlesex County and certain other areas in Massachusetts. This exemption was granted in accordance with, and is subject to, the provisions of 40 CFR Part 166, issued December 3, 1973 (38 FR 33303), which prescribes requirements for exemption of Federal authority for use of pesticides under emergency conditions.

This notice contains a summary of certain information required by regulation to be included in the notice. For more detailed information, interested
NOTICES

The Final Environmental Impact Statement (FEIS) for the proposed Pebble Mine in southwest Alaska has been released by the Minerals Management Service (MMS). The FEIS analyzes the potential impacts of the Pebble Mine project on the natural and cultural resources of Alaska. The public is invited to comment on the FEIS before October 21, 1976.

Insecticide per acre. No more than 3 applications will be made on any given field to the extent and in the manner set forth in the application. The specific exemption is also subject to the following restrictions:

1. The acreage to be treated with azinphos methyl (Guthion) is limited to thirty (30) acres.
2. Guthion (Guthion) will be applied with ground equipment.
3. The dosage rate may not exceed one-half (1/2) pound of actual azinphos methyl per acre per application.
4. The total amount of applications may not exceed three (3).
5. A thirty-five-day preharvest interval must be observed.
6. Carrot tops treated with azinphos methyl may not be used for food, feed, or forage.
7. A residue level not to exceed 0.5 ppm on carrot roots has been determined to be adequate to protect the public health. The Food and Drug Administration of the U.S. Department of Health, Education, and Welfare, has been advised of this action.
8. The Applicant is responsible for ensuring that the restrictions pursuant to this specific exemption are met.

Dated: September 2, 1976.

EDWIN L. JOHNSON, Deputy Assistant Administrator for Pesticide Programs.

NEVADA DIVISION OF HEALTH

Crisis Exemption Using DDT To Control Flea Vectors of Plague

Pursuant to the provisions of section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (38 Stat. 973; 7 U.S.C. 136), the Environmental Protection Agency (EPA) gives notice that the Nevada Division of Health, pursuant to an exemption, is permitted to use DDT to control fleas that may be vectors of plague in Nevada. The crisis exemption allows the use of DDT to control fleas that are vectors of plague in Nevada. The exemption is subject to the provisions of sections 166.2, 166.8, and 166.9 of the FIFRA Part 166. These regulations concern the exemption of Federal and State agencies for the use of pesticides under emergency conditions that were published in the Federal Register on December 3, 1973 (38 FR 33303). As required, the Applicant has submitted in writing the following certified information:

According to the Applicant, there was a bubonic plague outbreak in rodents at Nevada Beach at Lake Tahoe. At Nevada Beach, the roddents were again trapped and flea infestation determined. The percentage dropped, but not significantly, according to the Applicant; redusting of the burrows was required.

On July 22, the burrows were again dusted, using 25 pounds (5 cans) of DDT. Flea infestation showed a drop, but was still high. The Applicant decided to use DDT bait dust stations to assure better dusting of the rodents. On July 27, approximately 250 DDT bait dust stations were set, requiring 10 pounds of DDT. Flea infestation was checked on July 29, 1976; infestation dropped to a permissible level, and the Beach was permitted to reopen. The total amount of DDT used was 60 pounds (12 five-pound cans). Applications were made by trained personnel.

The official file concerning this exemption is available for inspection in the Office of Pesticide Programs, Room E-315, 401 M St., S.W., Washington, D.C. 20460.

Dated: September 2, 1976.

JOHN B. RITCH, JR., Director, Registration Division.

NEVADA cruse Exemption Using DDT To Control Flea Vectors of Plague

In FR Doc. 76-26284 Filed 9-8-76; 8:45 am

S. B. PENICK AND CO. ET AL.

Issuance of Experimental Use Permits

Correction

In FR Doc. 76-26284 appearing at page 36247 in the issue for Friday, August 27, 1976, on page 36248, in the first column, the first line should read as follows:

"No. 145-EUF-23 Thompson-Hayward"

ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

HIGH ENERGY PHYSICS ADVISORY PANEL

Meeting

Pursuant to the provisions of the Federal Advisory Committee Act, the High Energy Physics Advisory Panel (HEP AP) will meet September 27 and 28, 1976. The meeting will be held at the Energy Research and Development Administration offices at 400 First Street, N.W., Washington, D.C. in Conference Room 200. The portion of the meeting which will be open to the public will convene from 10 a.m. to approximately 6 p.m. on September 27, and will resume at 9 a.m. to approximately 11:30 a.m. on September 28.

The Panel will examine the current status of budget requests for the High Energy Physics Program; consider plans for future facility recommendations; discuss criteria for foreign travel and con-
visory Panel, Dr. Ernest Coleman, Div-
tutive Secretary, High Energy Physics

ten statements on the topics fo discus-
shall apply:
his judgment will facilitate the orderly
operation.
interference with Agency or Committee
which, if written would fall within ex-
subsection
throughout the end of the meeting at
ly 1
27;
prior to the open session on September

discuss the role of the High Energy Phys-
sider the research p~rogram and current
Big Accelerator on regional plans; con-
policies at national laboratories; discuss
conference delegations; consider computer

Panel will receive oral statements dur-
tunity to make oral statements concern-

To the Public Participation In
Topics to be

(a) Persons wishing to submit writ-
ten statements on the topics fo discus-
d by mailing 25 copies thereof, postmarked, if possible no later
than September 17, 1976, to the Execu-
tive Secretary, High Energy Physics Ad-
visory Panel, Dr. Ernest Coleman, Div-
ision of Physical Research, U.S. Energy
Research and Development Admin-
istration, Washington, D.C. 20550. Minutes
of the meeting will be kept open for 30 days
for receipt of written statements for the record.
(b) Those persons submitting a writ-
ten statement in accordance with para-
graph (a) above may request an oppor-
tunity to make oral statements concern-
ing the written statement, and shall set
forth reasons justifying the need for such
oral statements and their usefulness to the Panel. To the extent that the time
available for the meeting permits, the Panel
will receive oral statements during
a period of not more than 30 minutes
at an appropriate time, chosen by the
Chairman.
(c) Requests for the opportunity to
make oral statements shall be ruled on by
the Chairman of the Panel, who is
empowered to apportion the time avail-
able among those selected by him to
make oral statements.
(d) Information as to the Chairman’s
ruling on requests for the opportunity to
present oral statements, and the time
allotted, can be obtained by a prepa\ed telephones call on September 22, 1976, to
the office of the Executive Secretary of the Panel on (301) 353-3624 between 8:30 a.m. and 5 p.m. Eastern Time.
(e) Questions at the meeting may be
asked only by members of the Advisory
Panel.
(f) Seating for the public will be made
available on a first-come first-served
basis.
(g) The use of still, motion picture,
and television cameras, the physical in-
stallation and presence of which will not
interfere with Agency or Committee

The Chairman is empowered to con-
duct the meeting in a manner that in
his judgment will facilitate the orderly
conduction of business.

The Chairman will receive oral statements from persons in accordance with
paragraph (a) above by telephone call on September 22, 1976, or in writing on
September 26, 1976, to the Executive
Secretary, High Energy Physics Ad-
visory Panel, Dr. Ernest Coleman, Division
of Physical Research, U.S. Energy Research
and Development Administration, Wash-
ington, D.C. 20550. Minutes of the meeting will be kept open for 30 days
for receipt of written statements for the record.
Notice is hereby given that the Final Environmental Statement, ERDA-1546, Positron-Electron Storage Ring Project, Stanford Linear Accelerator Center, Stanford, California, was issued pursuant to the Energy Research and Develop-
ment Administration's (ERDA) implemen-
tation of the National Environmental Policy Act of 1969. The statement was prepared for the project which was included in the ERDA Fiscal Year 1976 Appropriations Act.
Copies of the final statement are available for public inspection in the ERDA public document rooms at:
ERDA Headquarters, 20 Massachusetts Avenue, NW., Washington, D.C.
Chicago Operations Office, 6500 South Cass Avenue, Argonne, IL.
Cincinnati Operations Office, 539 Second Street, Idaho Falls, ID.
San Francisco Operations Office, 1333 Broadway, Oakland, California.
Savannah River Operations Office, Savannah River Plant, Aiken, South Carolina.
Copies have been furnished to those who commented on the draft statement that was issued by the Energy Research and Development Administration.
FEDERAL COMMUNICATIONS
COMMISSION

AN INQUIRY RELATING TO THE COMMISSION'S RADIO OPERATOR LICENSING PROGRAM

Order Extending Time To File Comments and Reply Comments

Released: August 27, 1976.

1. The Electronic Industries Association's (EIA) Land Mobile Communications Section and the National Association of Broadcasters (NAB) have submitted requests for an extension of time within which Comments and Reply Comments in the above-captioned matter (41 FR 23881, June 8, 1976) might be filed.

2. Because of the importance and complexity of this proceeding, and because of the Commission's desire to obtain the widest possible response, an extension of time to November 1, 1976 for the filing of Comments and November 15, 1976 for the filing of Reply Comments is ordered, pursuant to section 3.311 of the Commission's rules.

C. PHYLL HORNE,
Chief, Filed Operations Bureau.
[FR Doc.76-20365 Filed 9-8-76; 8:45 am]

MIDWEST ST. LOUIS, INC. ST. LOUIS, MISSOURI; NEW LIFE EVANGELISTIC CENTER, INC. ST. LOUIS, MISSOURI

Applications for Construction Permit for a New Television Broadcast Station

MEMORANDUM OPINION AND ORDER

Adopted September 1, 1976;

By the Review Board: Board Member Kessler concurring in result. 1. This proceeding involves the mutually exclusive applications of Midwest St. Louis, Inc. (Midwest) and New Life Evangelistic Center, Inc. (New Life) for construction permits for a new television broadcast station to operate on Channel 24, St. Louis, Missouri. Now before the Review Board for consideration is a petition to enlarge issues, filed by New Life on July 29, 1976, which seeks to add "viability," Rule 1.65, lack of candor, and assentment issues against Midwest.

2. As relevant background, understanding the need for "viability" issues, the Board notes the following. At the time of designation, the Commission also had before it an application by Midwest for authorization to conduct subscription television (STV) operations over the facilities of its proposed station on Channel 24 and a mutually exclusive application for STV authority filed by Evans Broadcasting Corporation (Evans), licensee of Station Kdni-TV, St. Louis. The Commission decided that examination of the STV application of Midwest was not necessary to the basic comparison between Midwest and New Life, and that action on the Midwest STV application should be deferred pending the outcome of this hearing. It also stated that should Midwest prevail here, it would then undertake a comparative evaluation of the Midwest and Evans STV applications. However, it held that the STV programming proposal of Midwest could be compared with that of Evans and that the programming proposal of New Life under the standard comparative issue.

3. New Life submits that Midwest's application for a construction permit is an integral part of its overall proposal to operate an STV service in St. Louis, and that since Midwest has not applied simply for a construction permit and the Commission has not made the STV application part of this proceeding, a question arises as to the viability of Midwest's proposal. Indeed, New Life asserts, should Midwest prevail in this hearing, it may actually obtain an authorization for a facility it does not wish—a conventional television broadcast station. In support, New Life cites the transmittal letter submitted by Midwest to the Commission with its application which recites that Midwest's conventional and STV applications are "mutually contingent." Furthermore, New Life argues that Midwest's financial proposal contemplates an STV authorization and that the loan commitment upon which it relies is predicated on the construction of a television station and operation of an STV facility. Thus, New Life argues that Midwest has not made a financial or, for that matter, an ascertainment showing with respect to the operation of a conventional station and that it is not clear whether Midwest will operate at all unless it receives an STV authorization. New Life submits that issues are required to determine whether Midwest's conventional television application is a viable proposal. Whether Midwest can construct and operate a conventional facility irrespective of and pending its success in obtaining an STV authorization, and whether Midwest is financially qualified to operate the proposed facility pending and irrespective of receipt of an authorization for STV service. Finally, New Life states that the Board may wish to certify to the Commission the question of whether the Evans application for STV authority should be consolidated in this proceeding.

4. The Broadcast Bureau supports enlargement of the issues but states that the request for certification should be made in a separate pleading. Evans also opposes certification, essentially on the ground that the Commission should determine which of the two applicants for Channel 24 (New Life and Midwest) should receive a construction permit. In its opposition to the Board's Petition for Inquiry, Midwest agreed with New Life that certain "unnecessary" could result from the bifurcated hearing process adopted by the Commission such as Midwest being left with a construction permit it does not want should it prevail against New Life herein but lose subsequently to Evans in the STV comparative hearing. Midwest refers the Board to its Petition for Inquiry and Rulemaking filed with the Commission July 23, 1976, wherein it seeks reconsideration of Commission policy and establishment of uniform standards to govern designation in this area. Midwest also supports certification of the question regarding consolidation of the Evans application. Because it believes rulemaking rather than a mandatory hearing is the appropriate forum for these questions, Midwest opposes New Life's requested viability issue. Furthermore, Midwest states, in view of its representations in its pleadings to the Board and the Commission, there is no factual question requiring action as to whether it will construct and operate a conventional facility irrespective of its success.

5. Midwest relies on a letter of credit from its parent corporation to meet its total cash requirements. The letter states in pertinent part: This letter will advise your corporation (hereinafter "St. Louis") that Midwest Radio-Television, Inc. (hereinafter "WCTV") is prepared to advance to St. Louis as loans, through the purchase of your securities, or by guaranteeing loans from financial institutions, such sums as may be required for the processing of the St. Louis applications for a construction permit for the proposed television station in St. Louis and for STV authority for that market; for the construction and for the operation of the proposed television station in St. Louis and for the proposed television station in St. Louis. Hence, Midwest relies on a letter of credit from its parent corporation to meet its total cash requirements.

6. Midwest relies on a letter of credit from its parent corporation to meet its total cash requirements. The letter states in pertinent part: This letter will advise your corporation (hereinafter "St. Louis") that Midwest Radio-Television, Inc. (hereinafter "WCTV") is prepared to advance to St. Louis as loans, through the purchase of your securities, or by guaranteeing loans from financial institutions, such sums as may be required for the processing of the St. Louis applications for a construction permit for the proposed television station in St. Louis and for STV authority for that market; for the construction and for the operation of the proposed television station in St. Louis and for the proposed television station in St. Louis.
in obtaining STV authorization. Finally, Midwest asserts in view of the aforesaid mutual contingency of its conventional and STV applications, the question of whether Midwest would finance a conventional station even if it fails to receive STV authorization is purely hypothetical and its resolution irrelevant.

5. We see no need for issues concerning the viability of Midwest's application for a conventional television broadcast station, or concerning Midwest's intentions to construct a conventional television facility in the event it is unsuccessful in obtaining an authorization for subscription television operations. Although the applications for a basic construction permit and for authority to conduct STV operations have been filed separately, it is now perfectly clear that Midwest does not want any authorization which does not include authority for STV operations. This position is improper. The Commission's rules, see Section 73.642(a), 47 CFR 73.642(a), provide for the grant of an authorization for STV service to "an applicant for a construction permit for a new commercial television station, application...as well as to the licensee or permittee of a commercial television broadcast station. The only proviso is that an authorization for STV operations will be granted only upon the completion of the construction permit for the new station. Thus, while it is clear that an authorization for STV operations will not be issued unless the applicant is also basically qualified for a construction permit, there is no reason why the two applications cannot be considered together, and it is quite unrealistic, at least in the context of this case, to separate the two applications and judge Midwest upon the basis of something it is not in fact seeking and which the rules do not require it to seek—authority for a purely conventional operation. Since Midwest has now made its position unmistakably clear, there is no good reason to add issues concerning its intentions or its application for a construction permit without regard to its application for STV authority. Nor, for the same reason, is there any warrant for adding the additional issue sought by New Life for its application for a construction permit which Midwest is financially qualified to construct and operate a conventional television facility "pending and irrespective of" receipt of authority to operate a subscription television service.

6. We also believe, since Midwest's intentions have now been made clear, that we should certify to the Commission for its further consideration the question of whether the STV application of Midwest should be included in this hearing and the further question of whether the application of Evans for STV operation should also be considered in the same proceeding. In this connection, we note that while a grant to New Life in the present posture of the matter would create no uncertainties, the possibility that Midwest is to be preferred to New Life (assuming both parties are found basically qualified) could result in the unnecessary denial of the application of New Life and a grant to Midwest of something it does not seek (an authorization for a purely conventional operation) if Evans were later found superior to Midwest. Furthermore, concerns have been raised that Midwest may not be sufficiently familiar with STV considerations to compare New Life and Midwest in one proceeding and then to institute a new proceeding to compare Midwest and Evans. It is equally clear that the present hearing structure might not be the most efficient. The remedy would appear to be a simultaneous consideration of all of the pending applications, so that the Commission could determine in one hearing proceeding the grant or grants required by the public interest. Since it is beyond the power of the Board to achieve this result, and since we think the parties have presented problems which warrant further consideration, we will respectfully refer these questions to the Commission for its judgment.

7. In support of its requests for Rule 1.65 and lack of candor issues, New Life reiterates that on May 3, 1973, Midwest consummated an agreement with The Public Broadcasting Service Commission (St. Louis) on May 3, 1976, Robert Glazier, Executive Director of KETC-TV, the license of the station KETC-TV, for use of the latter's transmitter tower as Midwest's proposed antenna location for purposes of this application. However, New Life asserts, by letter dated December 20, 1975, Robert Glazier, Executive Director of St. Louis, advised Midwest that the agreement, which was due to expire May 2, 1976, could not be extended beyond that date "under any conditions." New Life contends that Midwest has failed to notify the Commission of this development and concludes that the significance of the change in availability of Midwest's proposed transmitter site and the applicant's dereliction in notifying the Commission of its judgment. In opposition, Midwest submits that its agreement with the Doody survey is not renegotiated. Until that time, Midwest asserts, it believed it could convince St. Louis to reconsider its disinclination to renew the agreement.

8. The Board will add a Rule 1.65 issue. We agree with New Life that the unavailability of an applicant's proposed transmitter site is a decisionally significant matter which must be reported within 30 days. Rule 1.65 by 29, 1976, 35 RR 2d 503 (Rev. Bd. 1975). Here, it is clear from the plain language of the correspondence from St. Louis to Midwest in December 1975 that Midwest failed to have reasonable assurance of its site until after June 26, 1976. Nevertheless, Midwest did not inform the Commission of these developments until July 29, 1976, subsequent to the filing of New Life's petition herein. Although Midwest claims it acted promptly after receiving notification from St. Louis that the agreement would not be renegotiated, we have difficulty accepting this explanation, absent evidentiary inquiry, in view of the language of Glazier's letters in December, 1975. Accordingly, we will specify a Rule 1.65 issue encompassing inquiry into the applicant's basic and/or comparative qualifications; in view of the scope of this issue, a separate lack of candor issue is unnecessary.

9. New Life's final request is for issues relating to the adequacy of Midwest's efforts to ascertain community needs and to ascertain STV programming needs. We shall dismiss New Life's allegations with respect to STV ascertainment since Midwest's STV application is not before this proceeding. With respect to Midwest's ascertainment of community problems, New Life initially alleges that Midwest failed to contact any group of significant interest. Since it is beyond the power of the Board to achieve this result, and since we think the parties have presented problems which warrant further consideration, we will respectfully refer these questions to the Commission for its judgment.

* * *

Specifically, petitioner refers to the U.S. Army Records Center located in St. Louis.

Petitioner derives these categories from the recent decision on Ascertainment of Community Problems by Broadcast Renewal Applicants, 67 FCC 2d 418, 35 RR 2d 1655 (1976).
10. The Board will add a general ascertainment issue. Before discussing the alleged inadequacy in Midwest's showing, we note that a prime deficiency in Midwest's showing is its failure, except for some rudimentary information as to population, education, and other general community characteristics, to provide the demographic composition of its proposed community of license called for by the Primer. Without a more specific breakdown of the governmental and economic activities, the public service organizations, and the other elements of the community that make it distinctive, we cannot be assured that the applicant's contracts are representative of the important groups in its community. See Primer, Q. and A. 4, 9, and 10; Robert Cousen Wagner, 38 FCC 2d 403, 55 RR 2d 1085 (Rev. Bd. 1972). Furthermore, as correctly noted by petitioner, significant groups which Midwest does indicate exist in St. Louis do not appear as adequately reflected in the community leader survey. Thus, although Midwest characterizes transportation as an important part of the St. Louis economy and states that St. Louis is the one purporting representative from each of these groups listed is not clearly a leader in the field. Similarly, although the manufacturing industry is stated to be an important activity by Midwest, no interviews with leaders representing this group were conducted. See Voice of Dixie, Inc., 45 FCC 2d 1027, 59 RR 2d 1127 (1976). Nor is it clear from the descriptions of some of the individuals listed by Midwest—e.g., "staff representative, UAW; office manager, League of Women Voters; store manager, Arrow Shirts"—that these persons are community leaders. Moreover, although Midwest argues in its opposition pleading that many of its 34 interviewees are active in more than one organization so that actually 58 significant groups are represented in its survey, the applicant has only cited the "primary" organization affiliations of these individuals and therefore it is impossible to conclude that a leader of each organization has been contracted. Outside of St. Louis, Midwest appears to have contacted purported leaders of two communities, St. Louis and Clayton; however, it has not explained why representatives of such nearly and apparently major communities as University City (1970 population 28,956), Ferguson (1970 population 28,915), and Kirkwood (1970 population 31,880) were not contacted. This would appear to violate Q. & A. 6 of the Primer. Finally, although Midwest lists a number of community problems ascertained from its survey, few of these appear to be reflected in its programming proposal, and the proposal itself is general and does not appear to treat with Q. & A. 28 of the Primer which requires specific information as to program description, time segment, frequency, and programming, and problem or problems treated. In sum, Midwest's ascertainment showing appears to be deficient in many important respects, and, consequently, we believe a general ascertainment issue is called for.

11. Accordingly, it is ordered, that the petition to enlarge issues, filed by New Life Educational Television Corporation, on June 21, 1976, is granted to the extent indicated herein, and is denied in all other respects.

12. It is further ordered, that the issues in this proceeding be included to the following:

(2) (e) To determine whether Midwest St. Louis, Inc. has violated Rule 1.65 by programming preferences.

The attention of any party in interest desiring to file pleadings concerning any pending TV translator application, pursuant to section 309(d) (1) of the Communications Act of 1934, as amended, is directed to § 1.589 (f) of the Commission's rules for provisions governing the time for filing, and other requirements relating to such pleadings.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

TV TRANSLATOR APPLICATIONS Ready and Available for Processing

Adopted: August 30, 1976.
Released: September 3, 1976.

By the Chief, Broadcast Bureau Notice is hereby given pursuant to §§ 1.572(c) and 1.573(d) of the Commission's rules, that on October 21, 1976, the TV translator applications listed in the attached Appendix will be considered as ready and available for processing. Pursuant to § 1.227(d) and § 1.931(b) of the Commission's rules, an application, in order to be considered with any application appearing on the attached list or with any other application on file by the close of business on October 21, 1976, which involves a conflict necessitating a hearing with any application on this list, must be substantially complete and submitted for filing at the offices of the Commission in Washington, D.C., by the close of business on October 21, 1976.

To the above notice, applications for licenses to provide TV translator service are invited.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

NOTICES

Federal Register, Vol. 41, No. 176—Thursday, September 9, 1976

Appendix

TV TRANSLATOR APPLICATIONS

Applications Ready and Available for Processing

Adopted: August 30, 1976.
Released: September 3, 1976.

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FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

Attachment.

WTV TV TRANSLATOR APPLICATIONS

BPTT-3042
New, Kirksville, Ohio
Educational Television Association of Metropolitan Cleveland
Req: Channel 69, 10 watts Primary: WVIZ(TV), Cleveland, Ohio

BPTT-3043
New, Willoughby Hills Area, Ohio
Educational Television Association of Metropolitan Cleveland
Req: Channel 63, 10 watts Primary: WVIZ(TV), Cleveland, Ohio

BPTT-3044
New, Chagrin Falls, Ohio
Educational Television Association of Metropolitan Cleveland
Req: Channel 65, 10 watts Primary: WVIZ(TV), Cleveland, Ohio

BPTT-3045
New, Gates, Ohio
Educational Television Association of Metropolitan Cleveland
Req: Channel 67, 10 watts Primary: WVIZ(TV), Cleveland, Ohio

BPTT-3046
New, Allentown, Burlington County, New Jersey
University of Utah
Req: Channel 67, 20 watts Primary: KUED(TV), Salt Lake City, Utah

BY THE CHIEF, BROADCAST BUREAU
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The attention of any party in interest desiring to file pleadings concerning any pending TV translator application, pursuant to section 309(d) (1) of the Communications Act of 1934, as amended, is directed to § 1.589(f) of the Commission’s rules for provisions governing the time for filing, and other requirements relating to such pleadings.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

NOTICES

Applications Ready and Available for Processing

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To the above notice, applications for licenses to provide TV translator service are invited.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.
BPTT-3049 New, Rushford, New York  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 56, 1 watt  
Primary: WNED(TV), Buffalo, New York

BPTT-3049 New, Allentown, New York  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 59, 10 watts  
Primary: WNED(TV), Buffalo, New York

BPTT-3050 New, Andover, New York  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 62, 10 watts  
Primary: WNED(TV), Buffalo, New York

BPTT-3051 New, Fillmore, New York  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 62, 1 watt  
Primary: WNED(TV), Buffalo, New York

BPTT-3052 New, Angelica, New York  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 65, 1 watt  
Primary: WNED(TV), Buffalo, New York

BPTT-3053 New, Bolivar, New York  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 65, 10 watts  
Primary: WNED(TV), Buffalo, New York

BPTT-3054 New, Centerville, (Belfast), New York  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 67, 100 watts  
Primary: WNED(TV), Buffalo, New York

BPTT-3055 New, Rapid City, South Dakota  
Wyeno Communications, Inc.  
Req: Channel 15, 100 watts  
Primary: KYCU(TV), Cheyenne, Wyoming

BPTT-5635A New, California Polytechnic State University, California  
Board of Cooperative Educational Services of Allegany County  
Req: Channel 7, 1 watt  
Primary: KCOY(TV), Santa Maria, California

BPTT-5637 New, Shell, Wyoming  
Shell TV Association  
Req: Channel 5, 1 watt  
Primary: KURL(TV), Billings, Montana

Application deleted from Public Notice released March 25, 1976, (Mimeo No. 62550, 41 FR 20924)
5. It appears that the continued operation of the subject cable television system without a certificate of compliance is in violation of our Rules since it was not lawfully carrying television broadcast signals prior to March 31, 1972, and has not obtained a certificate of compliance. At a minimum, former Section 74.1105 of the Rules—which was deleted with the adoption of the 1972 Cable Television Report and Order—required the operator of a proposed cable television system to notify the licensees of local television broadcast stations that cable service would be undertaken. No such notification has been shown by Washington County Utility District to have ever been served nor do Commission records reflect that notification. Additionally, five of the signals currently carried are inconsistent with Section 76.59 of the Rules. The system has neither conducted technical performance tests as required by Section 76.501 of the Rules, nor filed its annual reports as required by Section 76.501 et seq. Finally, Washington County Utility District, although it has had ample opportunity, has failed to respond to official Commission correspondence.

6. The Commission’s silence and failure to reply, counseled with its refusal to appear at the hearing and place to be specified above at a hearing to be held at a time and date to be specified, is in violation of our Rules since it was apparently not obtained a certificate of compliance. No such service would be undertaken.

7. At a minimum, former Section 74.1105 of the Commission’s Rules is inconsistent with Section 76.59 of the Rules, which was deleted with the adoption of the 1972 Cable Television Report and Order. Accordingly, it is ordered, That pursuant to section 252(e)(1) (A) (I) of the Energy Policy and Conservation Act (Pub. L. 94-163), notice is hereby provided of a meeting of Subcommittee C of the Industry Advisory Board (IAB) to the International Energy Agency (IEA) to be held on September 29, 1976, at the offices of Mobil Oil Corporation, 150 East 42nd Street, New York, New York, beginning at 10:00 a.m.

8. Notice of Conference


August 27, 1976.

Before Commissioners: Richard L. Dunham, Chairman; Don S. Smith, John R. Holloman III; and James O. Wait.

On July 29, 1976, Central Illinois Light Company (CILCO) submitted for filing increases in the wholesale rate schedules applicable to two municipals and one cooperative customer. Under the wholesale rate schedule MW-2, demand charge would be raised to $6.00/kVA for the first 1,000 kVA or less and $6.50/kVA for additional demand from the old rates of $2.50/kVA and $2.25/kVA, respectively. Energy charge would be raised to 1.50c/kWh for the first 300 kWh per kVA of demand and 0.20c/kWh thereafter from $.45/kWh and .80/kWh, respectively. A monthly charge of $90.00 has been instituted.

1. See the following table:
Under the wholesale rate schedule RWA-2, demand charge for the first 1,000 kVA or less will be raised to $4.50/kVA and for additional kVA would be raised to $4.40/kVA from the old rates of $2.40/kVA and $2.60/kVA, respectively. Energy charge would be raised to the same level as in MW-2. A monthly charge of $135.00 has been instituted. Billing demand under both schedules is subject to a 6% eleventh month clause. The maximum monthly demand in any month shall not be less than 1,000 kVA, up from 500 kVA previously.

Public notice of CILCO's increase was issued on August 5, 1976, with comments, protests or petitions to intervene due on or before August 17, 1976. On August 16, 1976, Petitions to Intervene were filed by the Village of Chatham (Chatham) and Corn Belt Electric Cooperative, Inc. (Cooperative).

Chatham and Cooperative state that they will be directly and adversely affected by CILCO's proposed changes, that their respective interests cannot be adequately represented by other parties and, therefore, they request to intervene in this proceeding.

Chatham maintains that CILCO's proposed revised charges will result in an increase in rates to Chatham of 68%, that such increase is excessive and may be unjust and unreasonable.

Cooperative contends 1) that the proposed increase of 48% applicable to its rates is unreasonably high; 2) that the proposed increase is based on the Period II future test year ending June 30, 1977, which is not required for applications involving rate increases less than $1 million; 3) that the proposed increase should be based upon an existing test year, 4) that the wholesale rate cost of service allocation should be based on a ratio of summer peaks rather than a ratio of the twelve month average peaks, and 5) that CILCO's proposed rate results in an unreasonable rate of return on common equity.

The Commission's review of CILCO's proposed rates indicates that CILCO's proposed rate increases have not been shown to be just and reasonable and, therefore may be unjust, unreasonable, unduly discriminatory or preferential and otherwise unlawful. Accordingly, the proposed rate increases should be accepted for filing and suspended for five months.

CILCO proposes an effective date, after five month suspension, of February 1, 1977 for its filed increases. Such effective date is not within the ninety days prescribed by Section 35.3 of the Commission's Rules and Regulations. Good cause exists to waive the ninety day requirement as provided in Section 35.3(b), but in light of Cooperative's request for five month suspension and our decision to grant it, such waiver is unnecessary.

The Commission finds: (1) CILCO's proposed rate increases should be accepted for filing and suspended for five months.

(2) Good cause exists to allow Chatham and Cooperative to intervene in this proceeding.

The Commission orders: (A) Supplements No. 2 and No. 3 to Rate Schedule FPC No. 17, Effective: November 1, 1976 and No. 3 to Rate Schedule FPC No. 18 and Supplements No. 3 and No. 4 to Rate Schedule FPC No. 19 are hereby accepted for filing and use thereof suspended for five months, or until February 1, 1977, at which time they may become effective, subject to refund, pending the outcome of the litigation thereon.

(B) Pursuant to the authority of the Federal Power Act, particularly Sections 205 and 206 thereof, the Commission's Rules of Practice and Procedure, and the Regulations under the Federal Power Act (CPA Chapter D, a public hearing shall be held concerning the justness and reasonableness of the rates, charges, terms, and conditions of service included in CILCO's FFC Electric Thrift MGS as proposed to be revised by the subject filings.

(C) The Staff shall prepare and serve top sheets on all parties for settlement purposes on or before February 1, 1977.

(D) A Presiding Administrative Law Judge to be designated by the Chief Administrative Judge for that purpose, (see 18 CFR 3.5 (d)), shall convene a settlement conference in this proceeding on a date certain within ten days after the service of top sheets by the Staff, in a hearing or conference room of the Federal Power Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426. Said Presiding Administrative Law Judge is hereby authorized to establish all procedural dates and to rule upon all motions (with the exceptions of petitions to intervene, motions to consolidate and sever, and motions to dismiss), as provided for in the Rules of Practice and Procedure.

(E) CILCO shall file monthly with the Commission the report on billing determinants and revenues collected under the presently effective rates and the proposed increased rates filed, as required by Section 35.19a of the Commission Regulations, 18 CFR Section 35.19a.

(F) Chatham and Cooperative are hereby notified to file petitions to intervene in this proceeding, Provided, however, that participation by them shall be limited to matters affecting asserted rights and interests as specifically set forth in their petitions to intervene and Provided, further, that the admission of these parties shall not be construed as recognition by the Commission that they might be aggrieved because of any order or orders entered in this proceeding.

(G) The Secretary shall cause prompt publication of this order to be made in the Federal Register and shall serve a copy thereof on the wholesale customers of CILCO.

By the Commission.

KENNETH F. PHELPS, Secretary.

[FR Doc. 76-20271 Filed 9-8-76; 8:14 am]
NOTICES

**MAINE ELECTRIC POWER CO.**

**Notice of Filing Revising Prior Filing**

August 31, 1976.


MEPCO formally filed a Power Purchase and Transmission Agreement between MEPCO and certain New England electric utilities whereby MEPCO will be responsible for all power it purchases from the New Brunswick Electric Power Commission (New Brunswick) under a "Unit Participation Agreement" (submitted in the May 4, 1976, filing) to these utilities in accordance with rates specified thereunder.

MEPCO requests that the rate supplement become effective retroactively as of May 24, 1976, and that the normal notice requirements of 16 C.F.R. 35.11 be waived. MEPCO further requests a waiver of the requirements of 18 C.F.R. 33.15 since the additional information is either unavailable or has already been submitted through other filings with the Commission.

A major objection of the NEP Protest and Petition to Intervene was directed toward a "refund charge" imposed on MEPCO by New Brunswick and passed on by MEPCO to NEP, among others. MEPCO informs the Commission that since the NEP Protest and Petition to Intervene was filed, New Brunswick has agreed that the subject refund charge is not a proper item of cost. MEPCO states that copies of the filing were sent to all participants in the Power Purchase Transmission Agreement.

Any person desiring to be heard or to protest said application should file a petition to intervene or protest with the Federal Power Commission, 255 North Capitol Street, N.W., Washington, D.C. 20426, in accordance with Sections 1.8 and 1.10 of the Commission's Rules of Practice and Procedure (18 C.F.R. 1.8, 1.10). All such petitions or protests should be filed on or before September 10, 1976. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

**KENNETH F. PLUMB, Secretary.

[FR Doc. 76-26279 Filed 9-8-76; 8:45 am]**

[Docket No. ER76-678]

**GULF ENERGY AND DEVELOPMENT CORP.**

**Notice of Extension of Procedural Date**

August 31, 1976.

On August 24, 1976, Staff Counsel filed a motion to extend the date, fixed by order issued May 27, 1976, for service of Staff Top Sheets in the above-designated proceeding.

Upon consideration, notice is hereby given that an extension of time is granted to and including September 17, 1976, within which Mr. Glasgow and Champlin Petroleum Company shall file the data required by Commission order.

**KENNETH F. PLUMB, Secretary.**

[FR Doc.76-26278 Filed 9-8-76;8:45 am]

[Docket No. RP76-3]

**MISSISSIPPI POWER & LIGHT CO.**

**Order Accepting for Filing and Suspending Proposed Rate Changes, Granting Interventions and Establishing Procedures; Electric Rates**

August 27, 1976.

Before Commissioners: Richard L. Dunham, Chairman; Don S. Smith, John H. Holoman III, and James G. Watt.

On July 20, 1976, Mississippi Power and Light Company (MPLCO) tendered for filing proposed changes in its wholesale electric rate schedules applicable to seven electric power associations at 69 delivery points and for municipalities, which proposed changes would result in an increase in annual revenues of

1See Attachment A for designations.
§3,321,383 (12.3%) based on the 12 month period ending August 31, 1977. Said increase is based on the cost of construction work in progress (CWITP) in rate base as requested by MPEL in its filing. The proposed effective date of the rate increase is September 1, 1976. For the reasons set forth in the petition, the Commission shall accept the proposed rate schedules for filing, suspend the proposed rates for three months, or until December 31, 1976, whichever is later, after subject to refund, require MPEL to file within sixty (60) days revised charges reflecting the elimination of CWITP from rate base, and establish hearing procedures.

MPEL asserts that the principal reason for the increase in rates is that jurisdictional revenues at present rates are inadequate to meet cost of service and provide fair rate of return. MPEL further asserts that the required increase reflects a rate of return of 10.17% which is the minimum return required to carry the obligations to its investors and attract necessary additional capital to serve the future electric requirements of its customers. MPEL asserts that the inclusion of CWITP in rate base is justified in that over 60% of the CWITP included in its rate base for period II represents projects relating to the conversion of existing generating units from gas to oil, and as such do not produce future revenue, and in that it anticipates a favorable ruling in the rulemaking proceeding in Docket No. RM75-13 which would allow all CWITP in rate base by the time the subject increased rates would be allowed to go into effect.

Public notice of MPEL's proposed increase was issued on August 17, 1976 with comments, protests or petitions to intervene due on or before August 25, 1976. On August 20, 1976, a protest, petition to intervene, and request for hearing and five month suspension was filed by the seven electric power associations and five municipalities (hereinafter referred to as petitioners) being served under the rate schedule proposed for change as described above. Said petitioners state that they will be directly and adversely affected by MPEL's proposed changes which cannot be represented adequately by other parties, and therefore, they request to intervene in the proceeding. Petitioners allege that: (1) the proposed increased rates tend to MPEL for filing on July 30, 1976, are unjust and unreasonable because they are excessive; (2) several errors in the MPEL filing indiscriminately inflate the cost of service to petitioners; and (3) the proposed increased rates to them are discriminatory and anticompetitive, representing a "price squeeze" which violates the antitrust laws as recognized in FPC v. Conway Corp., 44 U.S.L.W. 4777.

Commission review of MPEL's proposed rate filing indicates the improper inclusion of CWITP in rate base in cost of service calculations. The Commission's review indicates that that proposed increased rates filed July 30, 1976 have not been shown to be just and reasonable and may be unjust, unreasonable, unduly discriminatory, preferential or otherwise unlawful. Many of the issues raised in the protest and petition to intervene by MPEL's wholesale customers are properly the subject for further development and consideration at hearing rather than at this state of the proceeding. The decision to suspend is discretionary and the Commission does not believe a full five month suspension is warranted.

Recent Commission decisions have made it clear that the Commission will not currently allow utilities to base rates upon the inclusion of CWITP in rate base.² As we stated in the Order Denying Application For Rehearing, Georgia Power Company, Docket No. E-9091, issued September 19, 1976:

The majority rule of public utility regulation holds that the value of plant under construction cannot be included in the rate base until the plant is "used and useful" in providing service to jurisdictional customers. We have consistently applied the "used and useful" rule throughout our formally reported final decisions. Statement of Accounts for public utilities and licenses makes clearly reflects that principle, although it has not been formally codified in a separate regulation, as in the case for gas pipeline companies, Sec. 164.631, 18 CFR.

We note that while it has not been the policy of this Commission to permit utilities to earn a return on useful but not currently in service calculations. 


(2) Good cause exists to require MPEL to file within sixty days of the issuance of this order revised rates and charges reflecting the elimination of CWITP from rate base.

(3) Good cause exists to allow the above-named petitioners to intervene in these proceedings subject to the rules and regulations of the Commission; Provided, however, that participation of such intervenors shall be limited to matters affecting asserted rights and interests as specifically set forth in the petition to intervene; and Provided further, That the admission of such intervenors shall not be construed as recognition by the Commission that it might be suggested because of any order or orders of the Commission entered in this proceeding.

(4) The Secretary shall cause prompt publication of this order to be made in the FEDERAL REGISTER.

By the Commission.

KENNETH F. PLUMS, Secretary.
ATTACHMENT A—MISSISSIPPI POWER & LIGHT COMPANY

RATES SCHEDULE MV-14

Rate schedule designations: (municipal)
(1) Supplement No. 6 Canton, Miss.
to rate schedule FPC No. 88 (supersedes supplement No. 5).
(2) Supplement No. 6 Kosciusko, Miss.
to rate schedule FPC No. 87 (supersedes supplement No. 5).

Rate schedule REA-14

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FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
NOTICES

[FR Doc.76-36328 Filed 9-8-76; 8:45 am]

NORTHERN NATURAL GAS CO. OPERATING AS PEOPLES NATURAL GAS DIVISION

Order Providing for Formal Hearing, Consolidating Proceedings, Granting Petitions To Intervene, and Prescribing Procedures

August 31, 1976.

Before Commissioners: Richard L. Dunham, Chairman; Don S. Smith, John H. Holloman III, and James G. Watt.

On August 11, 1976, Northern Natural Gas Company (Northern) filed an application in Docket No. CP76-52 pursuant to Section 7(c) of the Natural Gas Act for a certificate of public convenience and necessity authorizing the transportation of vaporized liquid natural gas (LNG) for its Peoples Natural Gas Division (Peoples) and the construction and operation of certain interconnection facilities. On November 29, 1976, an application, as amended, in which Northern alleged that the proposed facilities do not fall within this definition, was filed by Northern on behalf of Peoples requesting a declaratory order disclaiming jurisdiction or, in the alternative, an order directing issuance of a certificate of public convenience and necessity pursuant to Section 7(c) of the Act authorizing Peoples to construct and operate facilities for the liquefaction, storage and vaporization of natural gas in Hancock County, Iowa.

The applications indicate that Peoples is planning to construct an LNG plant with a net storage capacity of 1.5 million Mcf equivalent of varropyro natural gas and a sendout design rate of 50,000 Mcf per day. The plant is proposed to be located on land located approximately 4 miles south of Northern's Ventura Compressor Station in Hancock County. Northern states that the plant would be used for peak shaving during the heating season.

Northern states in its application in Docket No. CP76-52 that the proposed LNG facility is designed and would be used to aid and assist Peoples in the local distribution of natural gas in Iowa, Nebraska, and Minnesota. The approximate cost of the proposed LNG plant is $28,406,350. Northern alleges that volumes of gas to be made available to the LNG facility in the summer for liquefaction would be volumes within Peoples' authorized contract demand from Northern of 436,507 Mcf per day. The application states that the volumes which would be made available from the facility during the winter would, by displacement, be utilized in the various distribution systems operated by Peoples for sale and delivery to residential and small volume consumers.

Northern alleges that the proposed LNG plant is nonjurisdictional under Section 1(b) of the Natural Gas Act as a facility used for local distribution of natural gas. Northern maintains that even though the facility is designed and would be used to assist Peoples in the distribution of gas in Iowa, Nebraska and Minnesota, such facility would not be used for local distribution within those states and would not be used for the transportation of natural gas in interstate commerce.

Northern requests a declaratory order over said facilities or in the alternative certificate authorization therefor.

In Docket No. CP76-52, Northern requests a certificate of public convenience and necessity authorizing the transportation of LNG for Peoples and the construction and operation of certain interconnection facilities. Interconnection facilities are estimated to cost $310,000 which would be reimbursed by Peoples.

Thirteen customers of Northern have petitioned to intervene in these proceedings. Several petitioners voice concern that approval of the proposed LNG plant and interconnection facilities may increase the risk of curtailment to existing customers by allowing Peoples to provide service to new, higher priority customers during periods of gas shortages. In addition, on January 9, 1976, the Brick People, et al., filed a document entitled protest, petition to intervene out of time and request for formal hearing in Docket No. CP76-52, as well as a motion to consolidate for hearing the applications in Docket Nos. CP76-52 and CP76-166. The Brick People, et al., state in their petition in Docket No. CP76-52 that Northern's application therein for authorization to construct certain interconnection facilities and to transport LNG is contingent upon Peoples building an LNG plant in Hancock County. The Brick People, et al., allege that they are the owners of the proposed facilities and that the proceeding is nonjurisdictional under Section 1(b) of the Act, contending that there is nothing "local" about said proposed plant or its operations. The motion asserts that both proceedings involve common questions of law and fact and should be consolidated for formal hearing.

Section 1(b) of the Natural Gas Act states that the provisions of the Act shall apply to the transportation of natural gas in interstate commerce but exempts from Commission jurisdiction the local distribution of natural gas. The application in Docket No. CP76-166 indicates that the proposed LNG plant is designed and will be used to assist Peoples in the distribution of natural gas to consumers in three states. Northern argues that the Commission should declare the LNG facility exempt from jurisdiction since it would be involved in "local" distribution of gas and because Peoples' rates are regulated with respect to state and local jurisdiction.

Under the Natural Gas Act either transportation of natural gas in interstate commerce, or an LNG plant in interstate commerce for resale is sufficient to confer jurisdiction upon the Commission. Moreover, Section 5(b) of the Act recognizes that a company may be a "natural gas company" in cases where its rates may not be subject to the Commission's jurisdiction. In light of the foregoing statutory provisions of the Natural Gas Act and the legal and factual issues that have been raised to Northern's request for a declaratory order, we decline to issue a declaratory order. Northern and/or Peoples will be afforded an opportunity in the formal hearing hereafter scheduled to present evidence and argument in support of their contentions that the proposed facilities do not fall within this Commission's jurisdiction.

* * *

NOTICES

The proposal in Docket No. CP76-52 to construct interconnective facilities to the proposed LNG facility and request for transportation authorization are intrinsically related with the proposal in the application in Docket No. CP76-166. Common questions of law and fact appear to exist sufficient to warrant consolidation of such applications. A formal hearing will be provided to develop, inter alia, a record regarding:

1. How does construction of the proposed LNG plant and interconnective facilities attached said plant to Northern's transmission facilities advance the public interest and necessity?
2. What customers and which markets will be served should the LNG plant and interconnection facilities be constructed?
3. What effect would such proposed construction and operation have on existing customers?
4. Who would pay the cost of the proposed facilities and service?
5. Explain the operational relationship between Northern Peoples' Division, identify which entity would construct and operate the LNG plant and describe how said entity would obtain gas to operate the LNG facility?
6. Identify Peoples' priority 1 peak day requirements and priority 1 daily contract demand supplied by Northern? Identify the maximum volume of gas which could be served by Peoples during a period of peak demand, with and without the proposed LNG facility?
7. Will any existing customers of Peoples receive less gas on an annual basis as a result of the LNG plant?
8. If new customers are proposed to be served what gas usages are proposed and are alternative fuels available to meet these needs? How does continued addition of new customers advance the public interest?

The application in Docket No. CP76-52 was noticed on August 29, 1976, with interventions due by September 15, 1976. The application in Docket No. CP76-166 was noticed on December 18, 1976, with interventions due by January 9, 1976. The following petitions to intervene have been filed:

- City of Duluth, Minn., Sept. 15, 1976
- Furnished Industries, Inc., Sept. 15, 1976
- Inter-City Gas Ltd., Sept. 18, 1976
- Interstate Power Co., Sept. 18, 1976
- Terra Electric Light & Power Co., Sept. 18, 1976
- Iowa Power & Light Co., Sept. 18, 1976
- Iowa Southern Utilities Co., Sept. 22, 1976
- The Brick People, et al., Jan. 9, 1976
- The People, et al., Sept. 17, 1976
- Wisconsin Gas Co., Sept. 17, 1976

On October 14, 1975, and January 9, 1976, The Iowa State Commerce Commission filed notices of intervention in Docket Nos. CP76-52 and CP76-166, respectively.

Petitioners to intervene and the Iowa State Commerce Commission indicate that they have interests in this proceeding that may not adequately be represented by existing parties.

Late petitions to intervene have been filed in Docket No. CP76-52 by Minnesota Gas Company and the Brick People, et al.; however, both petitioners have filed timely petitions to intervene in Docket No. CP76-166. A timely petition to intervene was filed in Docket No. CP76-52 by Iowa Electric Light and Power Company which conveyed a late petition to intervene in Docket No. CP76-166. A late notice of intervention was filed by Iowa State Commerce Commission in Docket No. CP76-52; however, a timely notice of intervention was filed by it in Docket No. CP76-166. A late petition to intervene was filed in Docket No. CP76-52 by City of Duluth, Minnesota, alleging that it had not determined until September 16, 1976, that Northern's application might affect its requirements. It is to determine whether the City of Duluth purchases all its gas from Northern. Petitioner states it does not have sufficient information to determine whether Northern's proposal will affect the City of Duluth's requirements.

It is necessary to consolidate the proceedings in Docket No. CP76-52 and CP76-166. A late petition to intervene was filed in Docket No. CP76-52 by City of Duluth, Minnesota, alleging that it had not determined until September 16, 1976, that Northern's application might affect its requirements. It is to determine whether the City of Duluth purchases all its gas from Northern. Petitioner states it does not have sufficient information to determine whether Northern's proposal will affect the City of Duluth's requirements.

The Commission finds:

1. That it is necessary and appropriate in carrying out the provisions of the Natural Gas Act that a public hearing be held on the matters involved and the issues presented in these proceedings as hereinbefore described.
2. That the public hearing be held on the matters involved and the issues presented in these proceedings as hereinbefore described.
3. That the public hearing be held on the matters involved and the issues presented in these proceedings as hereinbefore described.
4. That the public hearing be held on the matters involved and the issues presented in these proceedings as hereinbefore described.

The Commission orders:

(A) That the public hearing be held on the matters involved and the issues presented in these proceedings as hereinbefore described.
(B) That the public hearing be held on the matters involved and the issues presented in these proceedings as hereinbefore described.

By the Commission.

Kenneth F. Plumb, Secretary.

[FR Doc. 76-26260 Filed 8-9-76; 8:45 am]

[Docket Nos. RP72-156, (FGA76-3) and RP72-84 (DCA76-2)]

TEXAS GAS TRANSMISSION CORP.

Notice of Filing

August 30, 1976.

Take notice that on August 13, 1976, the Texas Gas Transmission Corporation (Texas Gas) tendered for filing a revised tariff sheet reflecting the exclusion of costs associated with small producers in excess of the "130 percent formula" prescribed in Opinion No. 742 and costs associated with emergency purchases at rates in excess of those prescribed in Opinion No. 742. All such costs were reflected in Texas Gas' filing of June 14, 1976. Texas Gas also filed a list of small producers from whom the company is purchasing gas at rates in excess of the "130 percent formula" prescribed in Opinion No. 742. As a consequence, with the Commission's order of July 30,
NOTICES

1976, whereby the Commission accepted the filing of June 14, 1976, and assigned to it an effective date of August 2, 1976.

Texas Gas states that copies of the filing have been sent to all of its customers as well as Interested State Commissions.

Any person desiring to be heard on or to protest said filing should file a petition to intervene or protest with the Federal Power Commission, 225 North Capitol Street, NE., Washington, D.C. 20426, in accordance with §§ 1.8 and 1.10 of the Commission's rules of practice and procedure (18 C.F.R. 1.8, 1.10). All such petitions-or protests should be filed on or before Sept. 10, 1976. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene with the Commission in accordance with the terms of the settlement agreement. The Commission in Docket No. RP75-75 (Advance Payments), et al., is made subject to the outcome of such litigation.

The Commission finds: (1) Transco's rate increase, filed July 16, 1976, has not been shown to be just and reasonable in that the advance payments upon which it is based have not been shown to be reasonable and appropriate.

(2) The lawfulness of Transco's instant rate increase as it relates to the advances made pursuant to agreements that are the subject of litigation in other docket is made subject to the outcome of those cases.

(3) The Commission should convene a hearing concerning the lawfulness of the advances contained in the instant filing made pursuant to agreements which have not been the subject of prior Commission litigation.

The Commission orders: (A) Transco's filing is accepted for filing to become effective September 1, 1976, subject to refund.

(B) A Presiding Administrative Law Judge, to be designated by the Chief Administrative Law Judge for that purpose (See Delegation of Authority, 18 C.F.R. 3.5 (d)), shall convene a prehearing conference in this proceeding on September 2, 1976, at 9:30 A.M., in a hearing room of the Federal Power Commission, 225 North Capitol Street, Washington, D.C. 20426. The issues in the proceeding shall be limited to the lawfulness of Transco's instant filing as it relates to advances made pursuant to agreements identified in footnote 3, supra. Said Presiding Administrative Law Judge is hereby authorized to establish all procedural dates and to rule upon all motions (with the exceptions of petitions to intervene, motions to consolidate and sever, and motions to dismiss), as provided for in the Rules of Practice and Procedure.

(3) The lawfulness of Transco's rate increase as it relates to advances made pursuant to agreements which are the subject of prior Commission litigation at Docket Nos. RP75-48, and 75-3 and Docket No. RP75-75 (Advance Payments), et al., is made subject to the outcome of such litigation.

NOTICES

1976, whereby the Commission accepted the filing of June 14, 1976, and assigned to it an effective date of August 2, 1976.

Texas Gas states that copies of the filing have been sent to all of its customers as well as Interested State Commissions.

Any person desiring to be heard on or to protest said filing should file a petition to intervene or protest with the Federal Power Commission, 225 North Capitol Street, NE., Washington, D.C. 20426, in accordance with §§ 1.8 and 1.10 of the Commission's rules of practice and procedure (18 C.F.R. 1.8, 1.10). All such petitions-or protests should be filed on or before Sept. 10, 1976. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene with the Commission in accordance with the terms of the settlement agreement. The Commission in Docket No. RP75-75 (Advance Payments), et al., is made subject to the outcome of such litigation.

The Commission finds: (1) Transco's rate increase, filed July 16, 1976, has not been shown to be just and reasonable in that the advance payments upon which it is based have not been shown to be reasonable and appropriate.

(2) The lawfulness of Transco's instant rate increase as it relates to the advances made pursuant to agreements that are the subject of litigation in other docket is made subject to the outcome of those cases.

(3) The Commission should convene a hearing concerning the lawfulness of the advances contained in the instant filing made pursuant to agreements which have not been the subject of prior Commission litigation.

The Commission orders: (A) Transco's filing is accepted for filing to become effective September 1, 1976, subject to refund.

(B) A Presiding Administrative Law Judge, to be designated by the Chief Administrative Law Judge for that purpose (See Delegation of Authority, 18 C.F.R. 3.5 (d)), shall convene a prehearing conference in this proceeding on September 2, 1976, at 9:30 A.M., in a hearing room of the Federal Power Commission, 225 North Capitol Street, Washington, D.C. 20426. The issues in the proceeding shall be limited to the lawfulness of Transco's instant filing as it relates to advances made pursuant to agreements identified in footnote 3, supra. Said Presiding Administrative Law Judge is hereby authorized to establish all procedural dates and to rule upon all motions (with the exceptions of petitions to intervene, motions to consolidate and sever, and motions to dismiss), as provided for in the Rules of Practice and Procedure.

(3) The lawfulness of Transco's rate increase as it relates to advances made pursuant to agreements which are the subject of prior Commission litigation at Docket Nos. RP75-48, and 75-3 and Docket No. RP75-75 (Advance Payments), et al., is made subject to the outcome of such litigation.
applicable; and the frequency with which the information is proposed to be collected.

Written comments on the proposed FTC and FEA requests — are invited from all interested persons, organizations, public interest groups, and affected businesses. Because of the limited amount of time GAO has to review the proposed requests (which is due on September 1, 1976) and FEA has to send comments to the Federal Register by September 1, 1976, GAO respectfully requests that all interested persons, organizations, public interest groups, and affected businesses submit written comments on or before September 1, 1976.

Further information may be obtained from Patty J. Stuart, of the Regulatory Reports Review Staff, 202-376-5425.

FEDERAL TRADE COMMISSION

FTC requests clearance of a new single time questionnaire to be sent to 23 insurance companies, 2 investment brokers, 8 mutual funds, 21 savings and loan associations, and 21 banks requesting information about advertising and marketing practices in connection with the establishment of Individual Retirement Accounts/Annuities (IRAs) created under the Pension Reform Act of 1974. FTC estimates respondent burden to average 12 hours for each of the 75 respondents who represent a sample of the respondent universe in each category.

FEDERAL ENERGY ADMINISTRATION

FEA requests clearance of two new schedules, Schedule B-Supplier and Independent, and Schedule C-Class of Accounts/Annuities (IRAs), to be held in a standby status and are required. The Emergency Petroleum Administration for Administration (EPA) to monitor price movements of No. 2 Heating Oil (API 2, 28.5/30), as amended by the Energy Policy and Conservation Act (P.L. 94-163) as amended by the Energy Policy and Conservation Act (P.L. 94-163) and appropriate regulations. FTC estimates respondent burden to average 8 1/2 hours per month per respondent. NORMAN P. HAY, Review Officer.

LEGAL SERVICES CORPORATION

BOARD OF DIRECTORS

Meeting

The next meeting of the Board of Directors of the Legal Services Corporation will be held on September 17-18, 1976 in the Auditorium of the D.C. Chapter of the American Red Cross, 20th and E Streets, Northwest, Washington, D.C.

The meeting will begin at 8:00 a.m. on both days and will be for the purpose of considering and acting on reports from the Board's Committees and the President of the Corporation.

The meeting is open to the public.

SEPTEMBER 7, 1976.

THOMAS EHRLICH, President.

TENTATIVE AGENDA, BOARD OF DIRECTORS

MEETING, SEPTEMBER 17-18, 1976

Auditorium, D.C. Chapter, American Red Cross, 20th and E Streets, Northwest, Washington, D.C.

1. Adoption of agenda.
3. Reports by committees:
   a. Regula
tions: (i) part 1617-class actions, (ii) part 1618—enforcement procedures, (iii) part 1619—public disclosure of recipient policies.
   b. Appropriations and audit; (i) investment policies, (ii) 1976 budget allocation, (iii) 1976 budget request.
   c. Provision of legal services.
   d. Report by the president: a. support centers.

5. Other business.

The meeting will begin at 9:00 a.m. on September 17, 1976, and will continue until about 5:00 p.m., with an adjournment for lunch. The meeting will continue on September 18, 1976, if necessary. The Board will hold a brief executive session to discuss personnel matters and continuing litigation at lunch on September 17. The film on legal services sponsored by the Corporation, the ABA Standing Committee on Legal Aid and Indigent Defendants, and the National Legal Aid and Defender Association will be shown immediately after lunch at 2:00 p.m. on September 17.

[FR Doc.76-25547 Filed 9-8-76; 8:45 am]

LEGAL SERVICES CORPORATION

NOTICES

FUND FLORIDA LEGAL SERVICES, TALLAHASSEE.

Notice is hereby given that the intended grantees should have been Legal Services Corporation of North Florida, Tallahassee, Florida.

Additional information may be obtained by writing the Legal Services Corporation, 733 Fifteenth Street, NW, Suite 700, Washington, D.C. 20505.

THOMAS EHRLICH, President.

[FR Doc.76-25545 Filed 9-8-76; 8:45 am]

NATIONAL FOUNDATION ON THE ARTS AND THE HUMANITIES

National Endowment for the Humanities

ADVISORY COMMITTEE ON SCIENCE, TECHNOLOGY AND HUMAN VALUES

Meeting

In accordance with the Federal Advisory Committee Act, P.L. 92-663, the National Endowment for the Humanities announces the following meeting:

Name: Advisory Committee on Science, Technology and Human Values Meeting in Collaborative Session with the Advisory Committee on Ethical and Human Value Implications of Science and Technology, of the National Science Foundation.

Date: October 1, 1976.

Time: 9:30 a.m.

Place: Room 460, National Science Foundation, 1800 G Street, N.W., Washington, D.C.

Type of Meeting: Open.

Contact person: Dr. Richard Hedrich, Coordinator, Program of Science Technology and Human Values, Office of Planning and Analysis, National Endowment for the Humanities, Washington, D.C. 20506. (Telephone 202-336-1088.) Individuals planning to attend are requested to notify Dr. Hedrich by September 28.

Purpose of Advisory Committee: To provide advice and recommendations concerning support of scholarly activities in the field of ethical and human value relationships to developments in science and technology, in conjunction with cooperative programs of the National Endowment for the Humanities and the National Science Foundation.

AGENDA

Reports on recent program activities. Discussion of current patterns in college courses in science, technology and values. Discussion of international perspectives on science, technology and values field.

Review of program plans and priorities.

JOHN W. JORDAN, Advisory Committee Management Officer.

[FR Doc.76-25297 Filed 9-8-76; 8:45 am]

NUCLEAR REGULATORY COMMISSION

ADVISORY COMMITTEE ON REACTOR SAFEGUARDS SUBCOMMITTEE ON THE CLINCH RIVER BREEDER REACTOR

Meeting

In accordance with the purposes of Sections 29 and 32b of the Atomic Energy Act (42 U.S.C. 2061, 2062b), the ACRS Subcommittee on the Clinch River Breeder Reactor will meet on September 28-29, 1976 in the Auditorium of the
The Subcommittee will meet in closed Executive Session, with any of its consultants who may be present, to exchange opinions and discuss preliminary views and recommendations relating to the above review.

8:30 a.m. until the conclusion of business on September 28

The Subcommittee will hear presentations by representatives of the NRC Staff and the CRBR Project Office and will hold discussions with these groups pertinent to the review of the application for a permit to construct the Clinch River Breeder Reactor Plant. In particular, this review will concern aspects of structural design of the plant.

Wednesday, September 29, 1976
8:00 a.m.

The Subcommittee will meet in closed Executive Session, with any of its consultants who may be present, to exchange opinions and discuss preliminary views and recommendations relating to the above review.

8:30 a.m. until the close of business on September 29

The Subcommittee will hear additional presentations by representatives of the NRC Staff and the CRBR Project Office and will discuss aspects of a core disruptive accident.

At the conclusion of the open session on each day, the Subcommittee may caucus in a brief, closed session to determine whether the matters identified in the initial closed session have been adequately covered and whether the project is ready for review by the full Committee. During Valley Authority, and the Subcommittee members and consultants will discuss their final opinions and recommendations on these matters. Upon conclusion of the caucus, the Subcommittee may meet again in brief open session to announce its determination.

In addition to these closed deliberative sessions, it may be necessary for the Subcommittee to hold one or more closed sessions with the NRC Staff and applicants for the purpose of discussing confidential proprietary information.

I have determined, in accordance with Subsection 10(d) of Pub. L. 92-463, that it is necessary to conduct the above closed sessions to protect the free interchange of information at the final stages of the Subcommittee's deliberative process (5 U.S.C. 552(b)(6)) and to protect proprietary information (5 U.S.C. 552(b)(4)) and recommendations relating to the materials from individuals' advice, opinions, and recommendations while closed Executive Sessions are in progress is considered impractical.

Practical considerations may dictate alterations in the above agenda or schedule. The Chairman of the Subcommittee is empowered to conduct the meeting in a manner that, in his judgment, will facilitate the orderly conduct of business, including provisions to carry over an incomplete open session from one day to the next.

With respect to public participation in the open portion of the meeting, the following requirements shall apply:

(a) Persons wishing to submit written comments regarding the agenda may do so by providing 15 copies to the Subcommittee at the beginning of the meeting. Comments should be limited to safety-related areas within the Committee's purview.

Persons desiring to mail written comments may do so by sending a readily reproducible copy thereof in time for consideration at this meeting. Comments postmarked no later than September 21, 1976 to Mr. T. G. McCreless, ACRS, NRC, Washington, DC 20555 will normally be received in time to be considered at this meeting.

(b) Those persons wishing to make an oral statement at the meeting should make a written request to do so, identifying the topics and desired presentation time so that appropriate arrangements can be made. The Committee will receive oral statements on topics relevant to the Committee's purview at an appropriate time chosen by the Chairman of the Subcommittee.

Further information regarding topics to be discussed, whether the meeting has been cancelled or rescheduled, the Chairman's ruling on requests for the opportunity to present oral statements and the time allotted therefor can be obtained by a prior telephone call on September 27, 1976 to the Office of the Executive Director of the Committee (telephone 202/544-1374, Attn: Mr. T. G. McCreless) between 8:15 a.m. and 8:00 p.m. EDT.

(d) Questions may be propounded only by members of the Subcommittee and its consultants.

(e) The use of still, motion picture, and television cameras, the physical installation and presence of which will not interfere with the conduct of the meeting, will be permitted both before and after the meeting and during any recess. The use of such equipment will not, however, be allowed while the meeting is in session.

(1) Persons with agreements or orders permitting access to proprietary information, may attend portions of ACRS meetings where this material is being discussed upon confirmation that such agreements are effective and relate to the material being discussed.

The Executive Director of the ACRS should be informed of such an agreement at least three working days prior to the meeting so that the agreement can be confirmed and a determination can be made regarding the applicability of the agreement to the material that will be discussed during the meeting. Minimum information provided should include information regarding the date of the agreement, the scope of material included in the agreement, the project or projects involved, and the names and roles of the persons covered by the agreement. Additional information may be requested to identify the specific agreement involved. A copy of the executed agreement should be provided to Mr. T. G. McCreless of the ACRS Office, prior to the beginning of the meeting.

(2) A copy of the transcript of the open portion of the meeting will be available for inspection on or after the October 6, 1976 at the NRC Public Document Room, 1717 H St., N.W., Washington, DC 20555, at the Oak Ridge Public Library, Civic Center, Oak Ridge, TN 37830, and at the Lawson McGhee Public Library, 500 W. Church Street, Knoxville, TN 37902.

Copies of the minutes of the meeting will be made available for inspection on or after December 29, 1976. Copies may be obtained upon payment of appropriate charges.


JOHN G. HOYLE, Advisory Committee Management Officer.

ADVISORY COMMITTEE ON REACTOR SAFEGUARDS, SUBCOMMITTEE ON THE THREE MILE ISLAND NUCLEAR STATION, UNIT 2

Meeting

In accordance with the purposes of sections 29 and 182b. of the Atomic Energy Act (42 U.S.C. 2032, 2223b.), the ACRS Subcommittee on the Three Mile Island Nuclear Station, Unit 2, will meet on December 23, 1976 at the Quality Inn, 5680 Allentown Boulevard, Harrisburg, PA 17112. The purpose of this meeting is to review the application of the Metropolitan Edison Company for a license to operate Unit 2.

The agenda for subject meeting shall be as follows:

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Thursday, September 23, 1976, 1:00 p.m. The Subcommittee will meet in closed session, for which it will be in session, with any of its consultants who may be present, to exchange opinions and discuss preliminary views and recommendations relating to the above matters. The Subcommittee may meet again in brief open session to announce its determination. At the conclusion of the open session, the Subcommittee may caucus in a brief, closed session to determine whether the matters identified in the initial closed session have been adequately covered and whether the project is ready for review by the full Committee. During the session, Subcommittee members and consultants will discuss and recommend changes on these matters. Upon conclusion of this caucus, the Subcommittee may meet again in brief session to announce its determination.

In addition to these closed deliberative sessions, it may be necessary for the Subcommittee to hold one or more closed sessions with the NRC Staff and Applicant for the purpose of discussing confidential proprietary information.

I have determined, in accordance with subsection 10(d) of Pub. L. 92-463, that it is necessary to conduct the above closed sessions to protect the free interchange of internal views in the final stages of the Subcommittee's deliberative process (5 U.S.C. 552(b)(5) and protect proprietary information (5 U.S.C. 552(b)(4)). Separation of factual material from individuals' advice, opinions, and recommendations while closed Executive Sessions are in progress is considered impractical.

Practical considerations may dictate alterations in the above agenda or schedule. The Chairman, in his judgment, will facilitate the orderly conduct of business, including provisions to carry over an incompletely open session from one day to the next.

With respect to public participation in the open portion of the meeting, the following requirements shall apply:

(a) Persons wishing to submit written statements regarding the agenda may do so by providing 15 readily reproducible copies to the Subcommittee at the beginning of the meeting. Comments should be limited to safety-related areas within the Committee's purview.

Persons desiring to mail written comments may do so by sending a readily reproducible copy thereof in time for consideration at this meeting. Comments postmarked no later than September 17, 1976 to the Chairman, ACRS, NRC, Washington, DC 20555 will normally be received in time to be considered at this meeting.

Background information concerning items to be considered at this meeting can be found in documents on file and available for public inspection at the NRC Public Document Room, 1717 H St., N.W., Washington, DC 20555 and at the Government Publications Section, State Library of Pennsylvania, Box 1601 (Education Building), Harrisburg, PA 17126.

Copies of the minutes of the meeting will be made available for inspection at the NRC Public Document Room, 1717 H St., N.W., Washington, D.C. 20555 after December 24, 1976. Copies may be obtained upon payment of appropriate charges.

Dated: August 31, 1976,

JOHN C. HOLTZ, Advisory Committee, Management Officer.

[F DRC No. 76-29843 Filed 9-3-76; 8:46 am]

DOCKET NO. 50-261

CAROLINA POWER AND LIGHT CO. (H. B. ROBINSON STEAM ELECTRIC PLANT UNIT NO. 2)

Order for Modification of License

1. Carolina Power and Light Company (the Licensee), is the holder of Facility Operating License No. DPR-23 which authorizes the operation of a nuclear power reactor known as H. B. Robinson Steam Electric Plant Unit No. 2 (the facility) at steady state reactor power levels not in excess of 2300 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site near Hartsville, South Carolina.

II. In performance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on October 14, 1975, as supplemented by correspondence dated August 3 and 22, October 17, November 13, 18, and 24, 1975, the Technical Specifications issued December 3, 1975, for the facility limit the reactor total nuclear peaking factor (FP) to 2.30. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility and supplier of part of the nuclear fuel, to conform with the requirements of the Reactor Coolant Plant's ECCS Acceptance Criteria, 10 CFR Part 50, 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolant geometry and long term cooling. The total nuclear peaking factor limits for the Westinghouse fuel are also conservative for the nuclear fuel supplied by the Exxon Nuclear Corporation.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Additionally, upper head temperatures used in evaluating ECCS performance were assumed to

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be equal to the reactor inlet water temperature. Extensive sensitivity studies, submitted with previous calculations, demonstrated that the reactor outlet water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor outlet-water temperature differential (100% of the reactor outlet-water outlet differential) and to operate the facility at steady state reactor power equal to 20% of the reactor Inlet-water temperature such that if Fo is reduced by 20% the calculated peak clad temperature for the H. B. Robinson, Unit No. 2 reactor would exceed the Commission's ECCS performance criteria by about 200°F. The staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor inlet temperature (100% of the reactor outlet-reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The staff also directed the licensee to submit the following new provisions:

1. As soon as possible, the licensee shall submit an evaluation of ECCS cooling performance with appropriate correction for upper head water temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst-break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by about 40°F. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street NW, Washington, D.C. 20555, and at the Hartville Memorial Library, Home and Fifth Avenue, Hartselle, South Carolina 29550, (1) Licensee's letters of August 3 and 22, October 14 and November 13, 18, 24, 1975, (2) Amendment No. 15 to Facility License No. DPR-23, (3) Licensee's letter of August 18 and 25, 1976, and (4) 'This Order for Modification of License, In the Matter of Carolina Power and Light Company, H. B. Robinson Steam Electric Plant Unit No. 2, Docket No. 50-281.'

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, it is ordered that the licensee in accordance with the results of the above-mentioned evaluation for the facility located in the vicinity of Hartsville, South Carolina, as Zion Station, Units Nos. 1 and 2 (the "Licensee") at steady state reactor power levels not in excess of 3250 megawatts thermal (rated power). The facility consists of two pressurized water reactors (PWR) located at the Licensee's site near Zion, Illinois.

In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on September 3, 1974 and April 21, 1975, the technical specifications issued May 12, 1976 for the facilities limit the reactor total nuclear peaking factor (Fp) to 2.25 and 2.20 for Units Nos. 1 and 2, respectively. The ECCS performance evaluation submitted by the Licensee was based on a previously approved ECCS evaluation model developed by Westinghouse Electric Corporation (Westinghouse) for the facilities to conform to the criteria contained in 10 CFR Part 50, § 50.46 and Appendix E. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facilities' Technical Specifications, the ECCS cooling performance for the facility would conform to the criteria contained in 10 CFR Part 50, § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of relatively cooler reactor inlet water is ejected through a vent located on the periphery of the vessel to cool the upper portion of the head. Accordingly, upper head water temperatures were assumed in evaluating ECCS performance to be equal to reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is warmer than the reactor inlet water temperature, by about 60% of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst-break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by about 40°F. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.
N O T I C E S

[Docket Nos. 50-254, 50-265]

COMMONWEALTH EDISON CO. IOWA-IILLINOIS GAS AND ELECTRIC CO.
Issuance of Amendments to Facility Operating Licenses

The U.S. Nuclear Regulatory Commission (the Commission) has issued Amendment Nos. 30 and 29 to Facility Operating License Nos. DPR-29 and DPR-30, issued to Commonwealth Edison Company for itself and on behalf of the Iowa-Illinois Gas and Electric Company, which revised Technical Specifications for operation of the Quad Cities Station Unit Nos. 1 and 2 (the facility) located in Rock Island County, Illinois. The amendments are effective as of their date of issuance.

The amendments reassess the Technical Specifications contained in Appendices A and B of License Nos. DPR-29 and DPR-30 in their entirety as a separate document for each of the two units. Previously there was a single document applicable to both units. The format and section numbers of the reissued Technical Specifications have been revised to be consistent with current regulatory practice. There were no changes in requirements or limitations.

The application for these amendments complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations in 10 CFR parts 2, 51, 52, and 59. As a separate document for each of the two units, the amendments fully conforming to the requirements of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46(b) are to be provided for the facility as soon as possible. The additional limitations set forth in the order will provide reasonable assurance that the public health and safety will not be endangered.


III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's rules and regulations in 10 CFR Parts 2 and 50: It is ordered, That Facility Operating Licenses Nos. DPR-39 and DPR-48 are hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (FQ) shall be reduced to 2.21 and 2.16 for Units Nos. 1 and 2, respectively.

Dated at Bethesda, Md., this August 27, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCIEE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc 76-20618 Filed 8-8-76; 8:45 am]

For the Nuclear Regulatory Commission.

DENNIS L. ZEHMANN,
Chief, Operating Reactors Branch #2, Division of Operating Reactors.

[Docket No. 50-247]

CONSOLIDATED EDISON CO. OF NEW YORK, INC. (INDIAN POINT NUCLEAR GENERATING UNIT NO. 2)
Order for Modification of License

I. Consolidated Edison Company of New York, Inc. (the Licensee), is the holder of Facility Operating License No. DPR-26 which authorizes the operation of a nuclear power reactor known as Indian Point Nuclear Generating Unit No. 2 (the facility) at steady state reactor power levels not in excess of 2788 thermal megawatts. The facility is a pressurized water reactor (PWR) located on the Licensee's site in Westchester County, New York.

II. Evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility were submitted by the Licensee by letter dated September 6, 1974, as supplemented by letters dated October 21, 1974, November 6, 1974, December 2, 1974, January 6, 1975, April 21 and 29, 1975, May 21, 1975, July 9 and July 21, 1975, February 4, 9, and 19, 1976, April 22, 1976, May 27, 1976, June 14, 1976, and July 13 and 15, 1976. The Commission's Order issued December 27, 1974, for the facility limits the reactor nuclear peaking factor (FQ) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum clad oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than reactor outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in calculating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper
head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearing conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of this analysis indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission’s ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total, nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. These calculations will be in conformance with the Technical Specifications of the facility and the Public Document Room, available for public inspection in the Commission’s Public Document Room, 1717 H Street, NW. Washington, DC 20555 and at the Hendrick Hudson Free Library, 31 Albany Post Road, Montrose, New York.

Copies of the following documents are available for public inspection in the Commission’s Public Document Room, 1717 H Street, NW. Washington, DC 20555 and at the Hendrick Hudson Free Library, 31 Albany Post Road, Montrose, New York:

1. Letter from Consolidated Edison dated September 6, 1974, and supplement received on June 24, 1975
2. Letter from Consolidated Edison dated August 17, 1976
3. This Order for Modification of License, in the Matter of Consolidated Edison Company of New York, Inc., Lakeview Nuclear Generating Unit No. 2, Docket No. 50-286

As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated at Bethesda, Md., this 27th day of August 1976.

For the Nuclear Regulatory Commission,
BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-26168 Filed 9-8-76;8:45 am]

[Consolidated Edison Co. of New York, Inc., (the Licensee), is the holder of Facility Operating License No. DFR-64 which authorizes the operation of a nuclear power plant known as Indian Point Nuclear Generating Unit No. 3 (the facility) at steady state reactor power levels not in excess of 2760 thermal megawatts. The facility is a pressurized-water reactor located at the Licensee’s site in Westchester County, New York.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on October 10, 1975, November 12, 1975, March 11, 1976, and April 1, 1976, the Technical Specifications issued April 5, 1976, for the facility limit the reactor total nuclear peaking factor (Fp) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS cooling model developed by Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with requirements of the Commission’s ECCS Acceptance Criteria. These calculations, including those performed by Westinghouse, were based on the results of a worst case break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the analysis submitted for the Indian Point Unit No. 2 reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission’s ECCS performance criteria by about 8°F.

Extensive sensitivity studies, submitted with previous calculations submitted in connection with application of Westinghouse evaluation models, have resulted in a relationship between the reactor total nuclear peaking factor (Fp) and calculated peak clad temperature such that Fp is reduced by 0.01 the calculated peak clad temperature for the reactor would not exceed 220°F. As directed by the NRC staff, the licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.01 to 2.31. The staff believes that the licensee’s action, under the circumstances, is appropriate and that this provision should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that the total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission’s Public Document Room, 1717 H Street, NW, Washington, D.C., 20555 and at the Hendrick Hudson Free Library, 31 Albany Post Road, Montrose, New York:

1. Letter from Consolidated Edison dated October 6, 1974, and supplement received on June 24, 1975
2. Letter from Consolidated Edison dated August 17, 1976
3. This Order for Modification of License, in the Matter of Consolidated Edison Company of New York, Inc., Indian Point Nuclear Generating Unit No. 2, Docket No. 50-247

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FEDERAL REGISTER, VOL 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
As soon as possible, the licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (FQ) shall be reduced to 2.31.

Dated in Bethesda, Md., this 27th day of August 1976.

For the Nuclear Regulatory Commission.

A. Schwenke,
Chief, Operating Reactors Branch No. 1, Division of Operating Reactors.

[FR Doc.76-26164 Filed 9-8-76;8:45 am]

[Doc No. 50-294]

DUQUESNE LIGHT CO., ET AL. (BEAVER VALLEY POWER STATION UNIT NO. 1) - Order for Modification of License

I. Duquesne Light Company, Ohio Edison Company, and Pennsylvania Power and Light Company (the licensees), are the holders of Facility Operating Licenses Nos. DPR-55, DPR-47 and DPR-55, respectively, issued to Duquesne Light Company which revised Technical Specifications for operation of the Oconee Nuclear Station Units Nos. 1, 2, and 3, located in Oconee County, South Carolina. The amendments are effective as of the date of issuance.

The amendments establish provisions for implementing alternate measures to assure that liquid waste effluent release limits are met whenever liquid waste monitors cannot be set to properly alarm and control liquid releases.

The application for these amendments complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The amendments do not involve a significant environmental impact and that pursuant to 10 CFR 51.5(d) (4) an environmental impact statement, negative declaration, or environmental impact appraisal not be prepared in connection with issuance of these amendments.

For further details with respect to this action, see (1) the application for Modification of License dated April 10, 1976; (2) Amendments Nos. 1, 5, and 6 to Licensees Nos. DPR-55, DPR-47 and DPR-55, respectively, issued to Duquesne Light Company which revised Technical Specifications for operation of the Oconee Nuclear Station Units Nos. 1, 2, and 3, respectively, dated July 12, 1976; (3) the Commission's Safety Evaluation, Dated at Bethesda, Maryland, this 24th day of August 1976, for the Nuclear Regulatory Commission.

A. Schwenke,
Chief, Operating Reactors Branch No. 1, Division of Operating Reactors.

[FR Doc.76-26164 Filed 9-8-76;8:45 am]

[Doc No. 50-294]
total nuclear peaking factor reduced by 0.08 to 2.24. However, subsequent to the licensee's submittal, further review of data presented by Westinghouse has led the staff to conclude that an additional reduction in F_p over that presented by the licensee is warranted. This is based on the fact that the Westinghouse generic evaluation for plants with three reactor coolant loops, used the results from two different, but approved, ECCS models (the March 1975 and the October 1976 models). When consistent ECCS models are used the calculated peak clad temperature could increase by an additional 17°F.

After discussions with the NRC staff, on August 25, 1976, the licensee amended his previous submission to account for this additional increase in peak clad temperature, by reducing F_p to 2.22. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate, and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform with the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 7177 E Street, N.W., Washington, D.C. 20555 and at the Beaver Area Memorial Library, 100 College Avenue, Beaver, Pennsylvania 15009, (1) Licensee's Amendment No. 17 dated June 5, 1975, to his Application for an Operating License, (2) Facility Operating License including Appendix A (Technical Specifications) dated January 30, 1976, (3) Licensee's letters of August 18 and 25, 1976, and (4) this Order for Modification of License, In the Matter of Duquesne Light Company, Ohio Edison Company, and Pennsylvania Power Company, Beaver Valley Power Station, Unit No. 1, Docket No. 50-324.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, as amended, the Facility Operating License No. DPR-66 is hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for vessel outlet water temperature shall be reduced to 2.22.

For The Nuclear Regulatory Commission.

Dated in Bethesda, Md., this 27th day of August 1976.

Ben C. Reschke
Director, Office of Nuclear Reactor Regulation.

[FR Doc. 76-21612 Filed 9-8-76; 8:45 am]

Docket Nos. 50-250 and 50-251

FLORIDA POWER & LIGHT CO. (TURKEY POINT PLANT UNITS NOS. 3 AND 4)
Order for Modification of License

I. The Florida Power and Light Company (the Licensee), is the holder of Facility Operating Licenses No. DPR-31 and DPR-41 which authorize the operation of the nuclear power reactors known as Turkey Point Plant Units Nos. 3 and 4 (the facilities) at steady state reactor power levels not in excess of 2200 thermal megawatts. The facilities are pressurized water reactors (PWR) located at the Licensee's site in Dade County Florida.

II. In conformance with evaluations of the performance of the facilities' Emergency Core Cooling System (ECCS) submitted by the Licensee on March 10, 1975, and supplemented by letters dated April 10, April 29, May 15, and May 21, 1975, the Technical Specifications, issued June 5, 1975, for the facilities limit the reactor total nuclear peaking factor (F_p) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facilities. The calculations indicate that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 160°F.

III. Extensive sensitivity studies, submitted with previous calculations in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (F_p) and calculated peak clad temperature such that if F_p is reduced by 0.16 the calculated peak clad temperature for the Turkey Point Plant reactors would not exceed 2200°F.

As directed by the NRC staff, the Licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.16 to 2.16. However, subsequent to the licensee's submittal, further review of data presented by Westinghouse has led the staff to conclude that an additional reduction in F_p after that presented by the licensee is warranted. This is based on the fact that the Westinghouse generic evaluation for plants with three reactor coolant loops, used the results from two different, but approved, ECCS models (the March 1975 and the October 1976 models). When consistent ECCS models are used the calculated peak clad temperature could increase by an additional 50°F.

After discussions with the NRC staff, on August 24, 1976 the licensee amended his previous submission to account for this additional increase in peak clad temperature, by reducing F_p to 2.11. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved model with appropriate correction for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperatures, such...
calculations will demonstrate that operation with this total nuclear peaking factor would conform with the criteria of 10 CFR 50.46. Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C. 20555 and at the Environmental and Urban Affairs Library, Florida International University, Miami, Florida: (1) ECCS performance calculated in accordance with the approved Westinghouse Evaluation Model, (2) The evaluation of the effect on calculated peak cladding oxidation, maximum hydro-genol, coreall geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the perimeter of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance are assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this assumption, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak cladding oxidation, maximum hydrogenol, coreall geometry and long term cooling.

The evaluation submitted for the D.C. Cook Unit No. 1 reactor indicated that with this modification of the upper head water temperature the calculated peak cladding oxidation, maximum hydro-genol, coreall geometry and long term cooling would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations calculated in accordance with an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46. Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility continue to provide reasonable assurance that the public health and safety will not be endangered.

The International Atomic Energy Agency (IAEA) is developing a limited

Availabiity of Draft for Public Comment

The International Atomic Energy Agency (IAEA) is developing a limited

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number of internationally acceptable codes of practice and safety guides for nuclear power plants. These codes, and guides will be developed in the following five areas: Government Organization, Siting, Design, Operations and Quality Assurance. The purpose of these codes and guides is to provide IAEA guidance to countries beginning nuclear power programs.

The IAEA Codes of Practice and Safety Guides are developed in the following way. The IAEA receives and collates relevant existing information used by member countries. Using this collation as a starting point, an IAEA Working Group of a few experts then develops a preliminary draft. Following this, an IAEA Technical Review Committee reviews the preliminary draft and modifies it to the extent necessary to develop a draft acceptable to the IAEA Technical Review Committee. This draft Code of Practice or Safety Guide is then sent to the IAEA Senior Advisory Group which reviews and modifies the draft as necessary to reach agreement on the draft and then forwards it to the IAEA Secretariat to obtain comments from the member states.

As a part of this program Safety Guide SG-93, "Operational Limitations and Conditions" has been developed and the NRC staff is soliciting comments on this Guide from the U.S. public.

Ann IAEA Working Group, consisting of Mr. N. Vearravagaya of India, Mr. A. Higashi of Japan, and Mr. K. V. Seyfrit (Nuclear Regulatory Commission) of the United States developed the draft from an IAEA collation during a meeting that was held in Vienna, Austria on July 3-16, 1976.

As the next step in its development the draft Safety Guide is scheduled to be reviewed by the IAEA Technical Review Committee on Operations at a meeting in Vienna, Austria on October 4-8, 1976. Comments received by September 20, 1976 will be useful to this review. Single copies of this draft may be obtained upon request addressed to the Division of Operating Reactors, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555.

[NOTICES]

Promulgation of Amendment to Facility Operating Licenses

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FEDERAL REGISTER; VOL 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976

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NORTHERN LIGHT COMPANY, and Western Massachusetts Electric Company, which revised Technical Specifications for operation of the Millstone Nuclear Power Station, Unit No. 2, located in the Town of Waterford, Connecticut. The amendment is effective as of its date of issuance.

The amendment modifies the Technical Specifications to eliminate the required operability and surveillance of the Turbine Runback feature of the Engineered Safety Feature Activation System. The application for the amendment complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Ch. I, which are set forth in the license amendment. Notice of Proposed Issuance of Amendment to Facility Operating License in connection with this action was published in the Federal Register on July 22, 1976 (41 FR 30225). No request for a hearing or petition for leave to intervene was filed following notice of the proposed action.

The Commission has determined that the issuance of this amendment will not result in any significant environmental impact and that pursuant to 10 CFR 15.5(d)(4) an environmental impact statement, negative declaration or environmental impact appraisal need not be prepared in connection with issuance of this amendment.

For further details with respect to this action-see (1) the application for amendment dated August 4, 1976, (2) Amendment No. 17 to License No. DPR-65, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street N.W., Washington, D.C. and at the Waterford Public Library, Hope Perry Road, Waterford, Connecticut 06385.

A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 30th day of August 1976.

For the Nuclear Regulatory Commission.

GEORGE LEAR,
Chief, Operating Reactor Branch No. 3, Division of Operating Reactors.

NORTHERN LIGHT COMPANY, and Western Massachusetts Electric Company, which revised Technical Specifications for operation of the Millstone Nuclear Power Station, Unit No. 2, located in the Town of Waterford, Connecticut. The amendment is effective as of its date of issuance.

The amendment modifies the Technical Specifications to eliminate the required operability and surveillance of the Turbine Runback feature of the Engineered Safety Feature Activation System. The application for the amendment complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Ch. I, which are set forth in the license amendment. Notice of Proposed Issuance of Amendment to Facility Operating License in connection with this action was published in the Federal Register on July 22, 1976 (41 FR 30225). No request for a hearing or petition for leave to intervene was filed following notice of the proposed action.

The Commission has determined that the issuance of this amendment will not result in any significant environmental impact and that pursuant to 10 CFR 15.5(d)(4) an environmental impact statement, negative declaration or environmental impact appraisal need not be prepared in connection with issuance of this amendment.

For further details with respect to this action—see (1) the application for amendment dated August 4, 1976, (2) Amendment No. 17 to License No. DPR-65, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street N.W., Washington, D.C. and at the Waterford Public Library, Hope Perry Road, Waterford, Connecticut 06385.

A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 31st day of August 1976.

For the Nuclear Regulatory Commission.

GEORGE LEAR,
Chief, Operating Reactor Branch No. 3, Division of Operating Reactors.

NORTHERN LIGHT COMPANY, and Western Massachusetts Electric Company, which revised Technical Specifications for operation of the Millstone Nuclear Power Station, Unit No. 2, located in the Town of Waterford, Connecticut. The amendment is effective as of its date of issuance.
Facility Operating License Nos. DPR-42 and DPR-60 which authorize the operation of nuclear power reactors known as Prairie Island Nuclear Generating Plant Unit Nos. 1 and 2 (the facilities) at steady state power levels not in excess of 1650 thermal megawatts (rated power per Unit). The reactors are pressurized water reactors (PWR) located at the facility's site near Redwing, Minnesota. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facilities submitted by the Licensee on April 14, 1975, April 17, 1975, July 9, 1975, October 21, 1975, January 7, 1976, and March 1, 1976, the proposed Technical Specifications submitted by the Licensee on February 2, 1976 for the facilities limit the reactors total nuclear peaking factor to 9.15. The ECCS performance evaluation submitted by the Licensee was based upon previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facilities, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluations indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facilities' Technical Specifications, the ECCS cooling performance for the facilities would conform with the criteria contained in 10 CFR 50.46(b) which govern cooling performance. As soon as possible, the Licensee shall submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (90 percent of the reactor outlet-reactor inlet differential) and to operate the facilities in accordance with the results of this analysis. The results of the evaluation submitted for the Prairie Island reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facilities are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations would conform to the revisions of Appendix K to the requirements of 10 CFR 50.46 are to be provided for the facilities as soon as possible. The limitations presently incorporated in the Technical Specifications for the facilities continue to provide reasonable assurance that the public health and safety will not be endangered.


III. According to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, it is ordered, That Facility Operating License Nos. DPR-42 and DPR-60 are hereby amended by adding the following new provision:

As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Maryland this 27th day of August, 1976.

For the Nuclear Regulatory Commission,

Ben C. Fusche, Director, Office of Nuclear Reactor Regulation.

[FR Doc.75-26167 Filed 8-8-76; 8:45 am]

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
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[Docket No. 50-537]

PROJECT MANAGEMENT CORP. AND TENNESSEE VALLEY AUTHORITY (CLINCH RIVER BREEDER REACTOR PLANT)

Special Meeting With Counsel

August 31, 1976.

The Licensing Board will hold a special meeting with counsel to consider all matters related to the Memorandum and Order of the Nuclear Regulatory Commission dated August 27, 1976, in connection with Contentions 10 and 11 submitted by Intervenors NRDC, et al. Such meeting with counsel will be held on Thursday, September 23, 1976, at 10:00 a.m. at the Nuclear Regulatory Commission, Atomic Safety and Licensing Board Panel Office, 4th Floor, East-West Towers Bldg., 4350 East-West Highway, Bethesda, Maryland, to consider the following aspects of the Commission's Order:

1. Action consistent with the Memorandum and Order of the Commission entered August 27, 1976.
2. Schedule revisions or amendments.
3. The likelihood that the proposed CBRR project will meet its objectives within the IMFPB program, as a relevant issue.
4. Alternatives for meeting such objectives, evaluated in terms of the objectives defined in the ERDA Impact statement.
   (a) Alternatives sites outside the Tennessee Valley Authority service area.
5. Clarification of the subcontents of NRDC Contention 10.
6. Limitations on discovery and cross-examination, consistent with the standards described in the Commission's Memorandum and Order.
7. Other matters reasonably related to the foregoing subjects.

Counsel are requested to have any relevant papers they desire to submit in the offices of the Licensing Board at the above address on or before 4:00 p.m., Friday, September 17, 1976. It is so ordered.

Dated at Bethesda, Maryland, this 31st day of August, 1976.

ATOMIC SAFETY AND LICENSING BOARD,
MARSHALL E. MILLER,
Chairman.

[FR Doc. 76-28170 Filed 9-8-76; 8:45 am]

[Docket No. 50-537]

PUERTO RICO WATER RESOURCES AUTHORITY

Availability of Draft Environmental Statement (Spanish translation) for North Coast Nuclear Plant, Unit No. 1

Pursuant to the National Environmental Policy Act of 1969 and the United States Nuclear Regulatory Commission's regulations in 10 CFR Part 51, notice is hereby given that a Draft Environmental Statement (Spanish translation) has been prepared by the Commission's Office of Nuclear Reactor Regulation related to the suitability of the site proposed for construction of the North Coast Nuclear Plant, Unit No. 1.

Dated in San Juan, Puerto Rico, this 27th day of August, 1976.

M. I. REYES,
Chairman.

[FR Doc. 76-28153 Filed 9-8-76; 8:45 am]

[Docket No. 50-534]

PORTLAND GENERAL ELECTRIC CO., ET AL. (TROJAN NUCLEAR PLANT)

Order for Modification of License

I. The City of Eugene, Oregon and Pacific Power and Light Company (the Licensee) are the holder of Facility Operating License No. NPF-1 which authorizes the operation of a nuclear power reactor known as Trojan Nuclear Plant (the facility) at steady state reactor power levels not in excess of 3411 thermal megawatts (rated power). The facility is located at the licensee's site on the west side of the Columbia River in Columbia County, Oregon.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the licensee on November 4, 1974 and September 5, 1975, the Technical Specifications issued November 31, 1975 for the facility limit the reactor total nuclear peaking factor (Fp) to 2.32. The ECCS performance evaluations submitted by the Licensee were based upon a previously approved Westinghouse Evaluation of Facility Operating License No. NPF-1 which authorizes the operation of a nuclear power reactor known as Trojan Nuclear Plant (the facility) at steady state reactor power levels not in excess of 3411 thermal megawatts (rated power). The facility is located at the licensee's site on the west side of the Columbia River in Columbia County, Oregon.

III. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

IV. Due to the configuration of the Westinghouse reactor vessel design, a small portion of the reactor inlet water which is cooler than outlet water is directed through several nozzles located on the perimeter of the vessel head to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. Recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this assumption, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

V. In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The request was based upon a previously approved Westinghouse Evaluation of Facility Operating License No. NPF-1 which authorizes the operation of a nuclear power reactor known as Trojan Nuclear Plant (the facility) at steady state reactor power levels not in excess of 3411 thermal megawatts (rated power). The facility is located at the licensee's site on the west side of the Columbia River in Columbia County, Oregon.

VI. The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations will demonstrate that the calculations for the facility are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility will continue to provide reasonable assurance that the public health and safety will not be endangered.

VII. Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street NW, Washington, D.C. 20555 and at the Columbia County Courthouse, Law Library, Circuits Court, St. Helens, Oregon 97051:
   (1) the ECCS performance evaluations dated November 4, 1974 and September 5, 1975, and (4) this Order for Modification of License, In the Matter of Portland General Electric Company, The City of Eugene, Oregon.

Dated in Portland, Oregon, this 27th day of August, 1976.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.
For the Nuclear Regulatory Commission.

GEORGE W. KNIGHTON, Chief, Environmental Projects Branch 1, Division of Site Safety and Environmental Analysis.

[FR Doc.76-26146 Filed 9-8-76; 8:45 am]

REGULATORY GUIDE

Issuance and Availability

The Nuclear Regulatory Commission has issued a new guide in its Regulatory Guide Series. This series has been developed to describe and make available to the public staff of the Nuclear Regulatory Commission's regulations and, in some cases, to delineate techniques used by the staff in evaluating specific problems or postulated accidents and to provide guidance to applicants concerning certain of the information needed by the staff in its review of applications for permits and licenses.

Regulatory Guide 1.121, "Bases for Plugging Degraded PWR Steam Generator Tubes," describes a method acceptable to the Nuclear Regulatory Commission for establishing the limiting safe conditions of tubes degraded by steam radiation of steam generator tubes; beyond which defective tubes as established by inspection should be removed from service by welding plugs at each end of the tube. This guide applies only to pressurized water reactors.

Comments and suggestions in connection with (1) items for inclusion in guides currently being developed or (2) improvements in all published guides are encouraged at any time. Public comments on Regulatory Guide 1.121, will, however, be particularly useful in evaluating the need for an early revision if received by November 5, 1976.

Comments should be sent to the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Docking and Service Section.

Regulatory guides are available for inspection at the Commission's Public Document Room, 1717 H Street NW., Washington, D.C. Requests for single copies of issued guides (which may be reproduced) or for placement on an automatic distribution list for single copies of future guides should be made in writing to the Director, Office of Standards Development, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555. Telephone requests cannot be accommodated. Regulatory guides are not copyrighted and Commission approval is not required to reproduce them.

(Docket No. 50-244)

ROCHESTER GAS AND ELECTRIC CORP. AND R. E. GINNA NUCLEAR POWER PLANT

Order for Modification of License

I. The Rochester Gas and Electric Corporation (the Licensee), is the holder of Provisional Operating License No. DPR-18 which authorizes the operation of the Rochester Gas and Electric Corporation (the facility) at steady state reactor power levels not in excess of 1,820,000 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site near Rochester, New York.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on March 11, 1976, the Technical Specifications issued May 14, 1975 for the facility limit the reactor total nuclear peaking factor (FP) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation of nuclear power developed by the Electric Corporation (Westinghouse), the designer of the facility, to conform to the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECS cooling performance for the facility would conform to the criteria contained in 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of relatively cooler reactor inlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the head. Accordingly, upper head temperatures were assumed in evaluating ECCS performance to be equal to the reactor inlet water temperature. However, recent dynamic data generated at the cut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is warmer than the reactor inlet water temperature, by about 60 percent of the reactor inlet-reactor outlet temperature differential. This increase in upper head water temperature over that used in ECCS performance calculations would have the effect of increasing the calculated peak clad temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 8, 1976, Westinghouse presented generic evaluations of the effect of increasing the calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head

Dated at Rochester, Maryland this 30th day of August, 1976.

ROBERT B. MINGUSE, Director, Office of Standards Development.

[FR Doc.76-26168 Filed 9-8-76; 8:45 am]
water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor inlet-reactor outlet outlet differential. On August 12, 1976, the staff directed the licensee to submit an analysis similar to the Westinghouse analysis with the clearly conservative assumption of upper head water temperature at core radius (100% of the reactor inlet-reactor outlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the R. E. Ginna reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor outlet temperature, or assuming that the upper head water temperature equals reactor outlet temperature plus the total nuclear peaking factor limited as set forth above, and with the other limits set forth in the Technical Specifications for the facility. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, IT IS ORDERED THAT Provisional Operating License No. DPR-18 is hereby amended by adding the following new provision:

1. As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculations in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature. The reevaluation calculations shall conform to the requirements of 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry, and long term cooling.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the licensee on April 15, 1976, as supplemented May 1, May 20, June 6, June 9, and June 11, 1976, the Technical Specifications Issued June 16, 1975 for the facility limit the reactor total nuclear peaking factor (Fq) to 2.10 for each unit. The ECCS performance evaluations submitted by the licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse) for the Westinghouse Electric Corporation's Nuclear Power Plants with three reactor coolant loops, the Westinghouse generic evaluation for the Westinghouse Electric Corporation's Nuclear Power Plants with three reactor coolant loops. The Westinghouse generic evaluation for Surry Power Station, Units 1 and 2, which would conform to the criteria of 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry, and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is hotter than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head water temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60% of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad-temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature equal to reactor inlet water temperature by an amount equal to 75% of the reactor inlet-reactor outlet differential. On August 13, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100% of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Surry reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 230°F for Surry Unit 1 and 250°F for Surry Unit 2.

Extensive sensitivity studies, submitted with previous calculations in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (Fq) and calculated peak clad temperature such that if Fq is reduced by 0.25 for Surry Unit 1 and 0.23 for Unit 2 the calculated peak clad temperature for the Surry reactors would not exceed 220°F. As directed by the NRC staff, the licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.25 to 1.85 for Surry Unit 1 and 0.23 to 1.87 for Surry Unit 2. However, subsequent to the licensee's submittal, further review of data presented by Westinghouse has led the staff to conclude that an additional reduction in Fq over that presented by the licensee is warranted. This is based on the fact that the Westinghouse generic evaluation for plants with three reactor coolant loops, used the results from two different, but approved, ECCS models (the March 1975 and October 1975 models). When consistent ECCS models are used the calculated peak clad temperature could increase by an additional 30°F.

After discussions with the NRC staff, on August 24 and 25, 1976, the licensee amended his previous submission to account for this additional increase in peak clad temperature, by reducing Fq to 1.80 for Surry Unit 1 and 1.82 for Surry Unit 2. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that op-
eration with this total nuclear peaking factor would conform with the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR § 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.


The amendment would revise the Technical Specifications to eliminate the fuel residence time limit and alter the core power distribution limits to allow operation of Point Beach Unit No. 1 in core Cycle 5.

Prior to the issuance of the proposed license amendment, the Commission have made the findings required by the Atomic Energy Act of 1954, as amended (the Act) and the Commission’s Rules and Regulations.

By October 12, 1976 the licensees may file a request for a hearing and any person whose interest may be affected by this proceeding may file a request for a hearing in the form of a petition for leave to intervene with respect to the issuance of the amendment to the subject facility operating license. Petitions for leave to intervene must be filed under oath or affirmation in accordance with the provisions of Section 2.714 of 10 CFR Part 2 of the Commission’s regulations. A petition for leave to intervene must set forth the interest of the petitioner in the proceeding, how that interest may be affected by the results of the proceeding, and the petitioner’s contentions with respect to the proposed licensing action. Such petitions must be filed in accordance with the provisions of this Federal Register notice and Section 2.714, and must be filed with the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555. Attention: Docketing and Service Section, by the above date. A copy of the petition and/or request for a hearing should be sent to the Executive Legal Director, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, and to Mr. Bruce W. Churchill, Esq., Shaw, Pittman, Potts & Trowbridge, 1800 M Street, N.W., Washington, D.C. 20036, the attorney for the licensees. A petition for leave to intervene must be accompanied by a supporting affidavit which identifies the specific aspect or aspects of the proceeding as to which intervention is desired and specifies with particularity the facts on which the petitioner relies as to both his interest and his contentions with respect to each aspect on which intervention is requested. Petitions stating contentions relating only to matters outside the Commission’s jurisdiction will be denied.

All petitions will be acted upon by the Chairman of the Atomic Safety and Licensing Board Panel. Timely petitions will be considered to determine whether a hearing should be notified or another appropriate order, issued regarding the disposition of the petitions.

In the event that a hearing is held and a person is permitted to intervene, he becomes a party to the proceeding and has a right to participate fully in the conduct of the hearing. For example, he may present evidence and examine and cross-examine witnesses.

For further details with respect to this action, see the application for amendment dated July 30, 1976, which is available for public inspection at the Commission’s Public Document Room, 1717 H Street, N.W., Washington, D.C. and at the University of Wisconsin—Stevens Point Library, Stevens Point, Wisconsin 54481. The license amendment and the State Evaluation Report on which issued, may be inspected at the above locations and a copy may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555.

On behalf of the Atomic Safety and Licensing Board Panel, the chairperson and members, in their capacity as chairperson and members, respectively, of the Atomic Safety and Licensing Board Panel, the decision of the Atomic Safety and Licensing Board Panel is to file a request for a hearing, by the above date. A copy of the hearing should be sent to the Executive Legal Director, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, and to Mr. Bruce W. Churchill, Esq., Shaw, Pittman, Potts & Trowbridge, 1800 M Street, N.W., Washington, D.C. 20036, the attorney for the licensees. A petition for leave to intervene must be accompanied by a supporting affidavit which identifies the specific aspect or aspects of the proceeding as to which intervention is desired and specifies with particularity the facts on which the petitioner relies as to both his interest and his contentions with respect to each aspect on which intervention is requested. Petitions stating contentions relating only to matters outside the Commission’s jurisdiction will be denied.

All petitions will be acted upon by the Chairman of the Atomic Safety and Licensing Board Panel. Timely petitions will be considered to determine whether a hearing should be notified or another appropriate order, issued regarding the disposition of the petitions.

In the event that a hearing is held and a person is permitted to intervene, he becomes a party to the proceeding and has a right to participate fully in the conduct of the hearing. For example, he may present evidence and examine and cross-examine witnesses.

For further details with respect to this action, see the application for amendment dated July 30, 1976, which is available for public inspection at the Commission’s Public Document Room, 1717 H Street, N.W., Washington, D.C. and at the University of Wisconsin—Stevens Point Library, Stevens Point, Wisconsin 54481. The license amendment and the State Evaluation Report on which issued, may be inspected at the above locations and a copy may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555.

Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 1st day of September 1976.

For the Nuclear Regulatory Commission.

GEORGE L. LEAH, Chief, Operating Reactors Branch No. 3, Division of Operating Reactors.

[FR Doc. 76-26147 Filed 9-8-76; 8:45 am]

[Docket Nos. 50-260 50-280 60-280]

WISCONSIN ELECTRIC POWER CO. AND WISCONSIN MICHIGAN POWER CO. POINT BEACH NUCLEAR PLANT UNITS Nos. 1 AND 2

Order for Modification of License

I. The Wisconsin Electric Power Company and Wisconsin Michigan Power Company (the Licensees), and the holders of Facility Operating Licenses Nos. DPR-24 and DPR-27 which authorize the operation of two nuclear power reactors known as Point Beach Nuclear Plant, Units Nos. 1 and 2, respectively, (the facility) at steady state reactor power levels not in excess of 1518 thermal megawatts (rated power). The facility consists of two pressurized water reactors (PWR) located at the Licensees’s site near Two Creeks, Manitowoc County, Wisconsin.

In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on September 6, 1974, June 30, and October 6, 1976 and supplements dated May 7, November 5 and 26, 1976, and December 15 and 18, 1975, the Technical Specifications issued December 24, 1976 for the facility limit the reactor total nuclear peaking factor (Fp) to 2.33. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission’s ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility’s Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR § 50.46(b) which governs maximum pressurized core cladding temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.
Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 6% of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature of the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 76% of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor inlet temperature (100% of the reactor outlet-reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Point Beach reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equal reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR § 50.46 are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility continued to provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1171 N Street, N.W., Washington, D.C. 20555, and at the following libraries:

- Stevens Point Library, Stevens Point, Wisconsin
- (1) the applications for amendment dated September 6, 1974, June 24 and October 6, 1975, and supplements dated December 6, 1974, May 7, November 5 and 26, and December 15 and 16, 1975, to License Nos. DFR-24 and DFR-27, (3) Licensee's letter dated August 18, 1976, and (4) This Order for Modification of License, In the Matter of Wisconsin Electric Power Company and Wisconsin Michigan Power Company, Point Beach Nuclear Plant, Units Nos. 1 and 2, Docket Nos. 59-266 and 59-301.

Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, it is ordered that Facility Operating License Nos. DFR-27 and DFR-27, as amended, are hereby amended by adding the following new provision:

1. As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance operation in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Maryland this 27th day of August 1976.

For the Nuclear Regulatory Commission,

BEN C. RUSCHE, Director, Office of Nuclear Reactor Regulation.

[F.R. Doc. 76-21177 Filed 9-8-76; 8:46 a.m.]

[DOCKET No. 50-305]

WISCONSIN PUBLIC SERVICE CORP.
KEWAUNEE NUCLEAR POWER PLANT
Order for Modification of License

I. The Wisconsin Public Service Corporation (the licensee), is the holder of Facility Operating License No. DFR-43 which authorized the operation of a nuclear power reactor known as the Kewaunee Nuclear Power Plant (the facility) at steady state reactor power levels not in excess of 1650 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the licensee's site in Kewaunee County, Wisconsin.

II. Pursuant to the Commission's Order dated August 9, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor inlet temperature (100% of the reactor inlet-reactor outlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Kewaunee reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 400 °F.

Extensive sensitivity studies, provided with previous calculations submitted in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (FP) and calculated peak clad temperature such that a low peaking factor would reduce the calculated peak clad temperature for the Kewaunee reactor would not exceed 2200 °F.

As directed by the NRC staff, the licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.04 to 2.11. The staff believes that the licensee's action, under the circum-
I. In conformity with calculations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on February 20, 1976, the Technical Specifications issued on June 2, 1976 (Amendment No. 25), for the facility limit the allowable peak linear heat generation rate (LHGR) as set forth in Figure 8–1 of the Technical Specifications. The ECCS performance analysis submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by Exxon Nuclear Corporation (Exxon), the nuclear fuel vendor, to conform to the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with the peak LHGR limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance calculations would conform to the criteria contained in 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolant geometry and long term cooling.

Due to the configuration of the reactor vessel design, a small portion of relatively cooler inlet water is directed through a bypass gap in the inlet nozzles to cool the upper portion of the head. Accordingly, upper head temperatures were assumed in evaluating ECCS performance to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is warmer than the reactor inlet water temperature, by about some 60% of the reactor inlet-reactor outlet temperature difference in upper head water temperature over that used in ECCS performance calculations would have the effect of increasing the calculated peak clad temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse, the reactor designer, presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for several types of Westinghouse reaction designs using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75% of a reactor inlet-reactor outlet differential. On August 12, 1976, the staff directed the licensee to submit an analysis with the clearly conservative assumption of upper head water temperature being 75% higher than reactor inlet-reactor outlet differential and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Yankee Rowe reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the previously established worst break cases resulting from the preliminary calculations thus far performed, and will assume that ECCS performance at the facility will conform to all the criteria set forth in 10 CFR § 50.46(b).

After discussions with the NRC staff on August 26, 1976, the licensee amended his previous submission, to account for these uncertainties, by reducing the peak LHGR from 1.0 to 0.65 kW/ft for a total reduction of 0.35 kW/ft. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, such calculations will demonstrate that operation at the reduced peak LHGR would conform to the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR § 50.46 are to be provided for the facility as soon as possible.

The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. 20555; and at the Yankee Atomic Electric Company, 265 County Street, Greenfield, Massachusetts 01301.

YANKEE ATOMIC ELECTRIC CO., YANKEE NUCLEAR POWER STATION (YANKEE-Rowe)

Order for Modification of License

I. Yankee Atomic Electric Company, is the holder of a Plant Operating License No. DPR-3 which authorizes the operation of a nuclear power reactor known as Yankee Nuclear Power Station (Yankee-Rowe) (the facility) at steady state reactor power levels not in excess of 650 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site in Rowe, Franklin County, Massachusetts.

II. It is ordered, that Facility Operating License No. DPR-3 which authorizes the operation of the nuclear power reactor known as Yankee Nuclear Power Station (Yankee-Rowe) (the facility) at steady state reactor power levels not in excess of 600 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site in Rowe, Franklin County, Massachusetts.

It is ordered, that Facility Operating License No. DPR-3 is hereby amended by adding the following new provisions:

As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculations in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (FP) shall be reduced to 2.11.
submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved ECCS Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for allowable peak LDG (Table 8-1 in the Technical Specifications) shall be reduced by 0.85 Kw/ft.

Dated in Bethesda, Maryland this August 27, 1976.

For the Nuclear Regulatory Commission,

Ben C. Rusine, Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-2416 Filed 9-6-76; 8:45 am]

OFFICE OF MANAGEMENT AND BUDGET

CANCELEATION OF REPORTS

List of Requests

The following is a list of requests for clearance of reports intended for use in collecting information from the public received by the Office of Management and Budget on September 3, 1976 (44 FR 3509). The purpose of publishing this list in the Federal Register is to inform the public.

The list includes the title of each request received; the name of the agency sponsoring the proposed collection of information; the agency form number(s), if applicable; the frequency with which the information is proposed to be collected; the time of the reviewer or reviewing division within OMB, and an indication of who will be the respondents to the proposed collection.

Requests for extension which appear to raise no significant issues are to be approved after brief notice through this release.

Further information about the items on this daily list may be obtained from the Clearance Officer, Office of Management and Budget, Washington, D.C. 20503, (202-395-4529), or from the reviewer listed.

NEW FORMS

ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

Unit Operation Equipment Survey, single-time, Warren Topelus, 395-5672.

ACTION

Action Cost-Sharing Study Project Survey Instruments, single-time, project directors, staff, advisory council in action Project Housing, Vocational and Labor Division, Raynham, R., 395-3332.

DEPARTMENT OF AGRICULTURE


DEPARTMENT OF COMMERCE

Domestic and International Business Administration, Evaluation of DIDA Business Assistance programs, DIA-5007, single-time, users of DIDA services. Peterson, M. O., 395-5631.

Bureau of Census

Interview Questionnaire and Reconciliation Record, AIS-1970 national sample panels 2 and 6, AHS-534, annually, households in 50 PSUs, design, Sunderhauf, M. D., 395-6140.


DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE


Office of Education, National Evaluation of Title I Programs for Neglected and Delinquent Children in State Institutions, OC-318, single-time, state title I coordinator, teacher, students, Human Resources Division, Raynham, R., 395-3522.

Public Health Service, Survey of Attitudes Toward Advancements in Biomedical and Behavioral Research Technology, OASR 0105, single-time, 1000 households, national cross-section, George Hall, 395-6140.


DEPARTMENT OF LABOR

Employment and Training Administration, Job Corpsmember Participation in the 1970 Upward Bound, Research MA-18, single-time, Job Corps centers, Human Resources Division, R. C., 395-3522.

DEPARTMENT OF THE INTERIOR

Departmental and Other, Claim for Reimbursement of Federal Expenditure, on occasion, displaced persons applying for relocation benefits, Warren Topelus, 395-5622.

DEPARTMENT OF VETERANS ADMINISTRATION

Revisions

Obtaining Supplemental Information from Doctor or Hospital, FL29-SOIB, on occasion, doctor or hospital official, Warren Topelus, 395-5672.

DEPARTMENT OF COMMERCE

Economic Development Administration, Marketing and Capacity Information Reports, ED 230, annually, commercial and industrial firms, Warren Topelus, 395-4529.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of Education:


Application for Federal Assistance—Title IV, Civil Rights Act, OE 290, annually, LEA's, SEA's, Institutions of higher education, Lowry, R. L., 395-3772.

Social and Rehabilitation Services, Annual Statistical Report on Hearings, SR SNSCS105, semianually, State public assistance agencies, Sunderhauf, M. D., 395-6140.

Office of Education:

Application for Federal assistance (Non-construction Programs) Instructions for Parts A, Title IV, Public Law 92-318, OE 444, annually, LEA's, Lowry, R. L., 395-0772.

DEPARTMENT OF LABOR

Employment Standards Administration:


DEPARTMENT OF JUSTICE

U.S. CITIZENSHIP AND IMMIGRATION SERVICES

Deportation of Significant Experience, CSC 1201, on occasion, households in any geographic area in United States, Marsha Traynham, 395-5622.

List of College Courses, CSC 1292, on occasion, households in any geographic area in United States, Marsha Traynham, 395-2423.

DEPARTMENT OF COMMERCE

Economic Development Administration:

Borrower's Request for Equity Credit, ED 269, on occasion, business entities expanding or building new facilities, Warren Topelus, 395-5622.

Status of Payments on Project Accounts, ED 268, on occasion, business entities constructing new or expanded facilities, Warren Topelus, 395-5622.

Business Loan Project Inspection and Certification of Acceptable Loan Projects on occasion, business firms expanding or building new facilities, Warren Topelus, 395-5622.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Social and Rehabilitation Service:


Office of Education:

Application for Federal Assistance (Non-construction Programs) Instructions for Community Education, OE 482 annually, LEA's, SEA's, SWF's, Warren Topelus, 395-4529.

Social and Rehabilitation Service:

Administrative and Legal Actions on Questions of Suspected Fraud. Under Medical Assistance Programs, SBS NCSS 1; quarterly, State Medicaid (Title XXI) agencies, Human Resources Division, Warren Topelus, 395-3522.

PHILIP D. LARSEN, Budget and Management Officer.

[FR Doc.76-25117 Filed 9-7-76; 9:30 pm]

SEcurities AND EXCHANGE COMMISSION

SMITH, BARNEY EQUITY FUND, INC. AND SMITH, BARNEY INCOME AND GROWTH FUND, INC., 1245 AVENUE OF THE AMERICANS, NEW YORK, NEW YORK 10019

[Rel. No. 9418 (812-2663)]

Notice of Filing of Application Pursuant to Section 6(c) of the Act for an Order Exempting Certain Transactions From Section 22(d) of the Act

August 26, 1976.

Notice is hereby given that Smith, Barney Equity Fund, Inc. ("Equity") and
Smith, Barney Income and Growth Fund, Inc. ("Income and Growth"), both Maryland corporations registered under the Act as open-end diversified management companies (collectively "Funds" or "Applicants"), filed an application on May 31, 1976, and amendments thereto on July 20 and August 24, 1976, pursuant to Section 6(c) of the Investment Company Act of 1940 ("Act") for an order of exemption from Section 22(d) of the Act to the extent necessary to permit the Funds to implement a schedule of sales charges which will not apply to certain classes of persons. All interested persons are referred to the application on file with the Commission for a statement of the representations therein which are summarized below.

Equity has operated since its inception, and Income and Growth since May 1, 1971, as no-load funds offering shares at net asset value without any sales charge being paid by purchasers of shares. Smith, Barney, Harris Upham & Co. Incorporated (Smith Barney), and its predecessor Smith, Barney & Co. Incorporated, have acted as distributors of the Funds' shares and Smith, Barney Advisors, Inc., a wholly-owned subsidiary of Smith Barney, Harris Upham & Co. Incorporated, have acted as distributors of the Funds' shares. Smith, Barney, Advisors, Inc. has sub-advisory agreements with Smith Barney.

It is proposed that, in the future, sales charges will be imposed on sales of the Funds' shares. However, all shareholders of record as of a cut-off date (to be determined) would have the right to make additional investments in net asset value at any time without the imposition of any sales charge. Persons who were not shareholders prior to the cut-off date would be subject to sales charges. However, after such a person shall have been a shareholder continuously for 24 months, he may make additional investments in net asset value without any sales charge, provided he is a shareholder at the time of purchase.

Section 22(d) of the Act provides that registered investment companies issuing redeemable securities may sell theirredeemable securities may sell their shares only at a current offering price described in the prospectus. Section 6(c) provides, in part, that the Commission may conditionally or unconditionally exempt any person, security, or transaction, or any class or classes of persons, securities, or transactions, from any provision of the Act, if and to the extent that such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

The Fund has proposed that the Commission issue an order pursuant to Section 6(c) of the Act for an exemption from the provisions of Section 22(d) of the Act with respect to (1) pursuant to the sale of additional shares of the Funds without a sales charge to present shareholders of the Funds as of a record date to be set by the Boards of Directors of the Funds, and (2) pursuant to the sale of additional shares of the Funds without a sales charge to shareholders who have become and remain shareholders for 24 consecutive months subsequent to such record date and prior to the time of the purchase of such additional shares.

Applicants state that the distinction the proposed plan makes between existing shareholders and new shareholders is based on the difference in the cost of selling an additional share to a present shareholder and the cost of selling the first share to a non-shareholder. Applicants assert that no sales effort or explanation by salesmen is necessary for additional purchases by existing investors, and that, for new shareholders, shares purchased in the first 24 months will be available with a sales charge somewhat below that imposed by other funds with standard sales charges. With respect to group programs as permitted by Rule 22d-1 (a) and (b), which own shares prior to the cut-off date or which become and remain shareholders subsequent to the cut-off date for 24 consecutive months. Applicants contend that there is an absence of selling costs incurred in adding a new person to the persons for whose benefit such programs hold the shares, which justifies the non-imposition of a sales charge on the purchases of shares for the benefit of a new person covered by such a program.

Applicants assert that the proposed plan has certain benefits for existing shareholders, new shareholders, and the Funds themselves. For existing shareholders the "no-load" status of the Funds is preserved; new shareholders may invest at "no-load" after 24 months; and the Funds will have a broader and more effective sales effort to reverse a downtrend in sales and return to a positive cash flow. Finally, Applicants also contend that, by exempting one shareholder who has held shares for 24 months from future sales charges, interest and other term holders are encouraged and continuing compensation to salesmen when their services are no longer required is eliminated.

Notice is further given that any interested person may, not later than September 20, 1976, submit to the Commission in writing a request for a hearing on the matter accompanied by affidavits or in punctual the Rules and Regulations of the Commission.

The purpose of this conference is to release a report by the Advisory Committees on school desegregation progress in Newport News Public School Districts since 1971, which supplements a national report on school desegregation released by the Commission on August 24th.
Dated at Washington, D.C., September 8, 1976.

ISAAC T. CRESWELL, Jr.,
Advisory Committee Management Officer.

[FR Doc.76-26595 Filed 9-8-76;12:02 pm]

INTERSTATE COMMERCE COMMISSION
[Notice No. 159]
ASSIGNMENT OF HEARINGS
September 3, 1976.

Cases assigned for hearing, postponement, cancellation or oral argument appear below and will be published only once. This list contains prospective assignments only and does not include cases previously assigned hearing dates. The hearings will be on issues as presently reflected in the Official Docket of the Commission. An attempt will be made to publish notices of cancellation of hearings as promptly as possible, but interested parties should take appropriate steps to insure that they are notified of cancellation or postponements of hearings in which they are interested.

MC 189649 (Sub-No. 11), Robert L. Allen, DBA Allen Transport, now assigned October 13, 1976, at Boston, Mass. will be held on the Fifth Floor, 150 Causeway.

MC 141932 (Sub-No. 1), Solar Transport, Inc., now assigned October 14, 1976, at Boston, Mass. will be held on the Fifth Floor, 150 Causeway.

MC-P-12802, Terminal Transport Co., Inc.—Purchase—Goguen Transportation Co., Inc. and MC 22299 (Sub-No. 108), now assigned October 18, 1976, at Boston, Mass. will be held on the Fifth Floor, 150 Causeway.

H. G. Homme, Jr., Acting Secretary.

[AUGUST 27, 1976]

BURLINGTON NORTHERN, INC.—ABANDONMENT BETWEEN—WAVERLY AND MOUNT HOPE IN SPOKANE COUNTY, WASHINGTON

August 27, 1976.

The Interstate Commerce Commission hereby gives notice that its Environmental Affairs Staff has concluded that the proposed abandonment by Burlington Northern Inc. of its railroad between Waverly and Mount Hope in Spokane County, Wash., a distance of 9.7 miles, if approved by the Commission, does not constitute a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321 et seq., and that preparation of a detailed environmental impact statement will not be required under section 4332(2) (C) of the NEPA. It was concluded, among other things, that because of the small amount of traffic which would be diverted to motor carriers, no significant environmental impacts will result from the abandonment of the line. The Washington Department of Game has identified the right-of-way as valuable wildlife habitat for several species and recommends that the corridor be preserved for wildlife and wildlife-oriented recreation. Nevertheless, there are no economic development plans in the area dependent upon the subject line, abandonment would not have a serious adverse effect on rural and community development.

This conclusion is contained in a staff-prepared environmental threshold assessment survey, which is available on request to the Interstate Commerce Commission, Office of Proceedings, Washington, D.C. 20423; telephone 202-275-7011. Interested persons may comment on this matter by filing their statements in writing with the Interstate Commerce Commission, Washington, D.C., 20423, on or before October 8, 1976. It should be emphasized that the environmental threshold assessment survey represents an evaluation of the environmental issues in the proceeding and does not purport to resolve the issue of whether the present or future public convenience and necessity permit discontinuance of the line proposed for abandonment. Consequently, comments on the environmental study should be limited to discussion of the presence or absence of environmental impacts and reasonable alternatives.

ROBERT L. OSWALD,
Secretary.

[FR Doc.76-26395 Filed 9-8-76;8:45 am]

THE SALT LAKE CITY UNION DEPOT AND RAILROAD COMPANY ABANDONMENT OPERATIONS SALT LAKE RAILROAD STATION, SALT LAKE CITY, UTAH

August 31, 1976.

The Interstate Commerce Commission hereby gives notice that its Environmental Affairs Staff has concluded that the proposed abandonment by the Salt Lake City Union Depot and Railroad Company of its passenger depot and tracks and terminal facilities in Salt Lake City, Utah, if approved by the Commission, does not constitute a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321 et seq., and that preparation of a detailed environmental impact statement will not be required under section 4332(2) (C) of the NEPA. It was concluded, among other things, that service will continue to be provided on the line by the applicant's co-owners and, therefore, there will be no diversion of rail freight or passenger traffic. The Denver and Rio Grande line from Salt Lake City is to be acquired for preservation purposes by the State of Utah. It is expected that the building will be adapted to another use, possibly as a museum. The historic and architectural characteristics of the building will not be altered.

This conclusion is contained in a staff-prepared environmental threshold assessment survey, which is available on request to the Interstate Commerce Commission...
NOTICES

WESTERN MARYLAND RAILWAY COMPANY ABANDONMENT OF ITS MONT-BINGAMON BRANCH NEAR HENSHAW IN HARRISON COUNTY, WEST VIRGINIA

August 31, 1976.

The Interstate Commerce Commission hereby gives notice that its Environmental Affairs Staff has concluded that the proposed abandonment by the Western Maryland Railway Company (WM) of its line of railroad between Milepost 6.88 to the end of the line at Milepost 6.72, a distance of 0.16 miles, near Henshaw, all in Harrison County, West Virginia, if approved by the Commission, does not constitute a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321, et seq., and that preparation of a detailed environmental impact statement will not be required under section 4332(2) (C) of the NEPA.

It was concluded, among things, that the environmental impacts of the proposed action are considered insubstantial because no traffic has been handled on the line since 1963, and, therefore, no diversion of traffic is expected. Consequently, there will be no alterations in existing air quality, fuel consumption, or noise intrusions. In addition, no land use plans of economic or industrial importance exist in the affected area which are dependent upon that continued operation of the line. Western Maryland Railway Company will continue to maintain rail service to Williams Mines, an active coal mining area located immediately south of the subject right-of-way. Interest has been expressed in acquiring the right-of-way for recreational use.

This conclusion is contained in a staff-prepared environmental threshold assessment survey, which is available on request to the Interstate Commerce Commission, Office of Proceedings, Washington, D.C. 20423; telephone 202-275-7011.

Interested persons may comment on this matter by filing their statements in writing with the Interstate Commerce Commission, Washington, D.C. 20423, on or before October 12, 1976.

It should be emphasized that the environmental threshold assessment survey represents an evaluation of the environmental issues in the proceeding and does not purport to resolve the issue of whether the present or future public convenience and necessity permit discontinuance of the line proposed for abandonment. Consequently, comments on the environmental study should be limited to discussion of the presence or absence of environmental impacts and reasonable alternatives.

H. G. Homme, Jr.
Acting Secretary.

[FR Doc.76-26394 Filed 9-8-76;8:45 am]

[Notice AB 69 (Sub-No. 4)]

MOTOR CARRIER BOARD TRANSFER PROCEEDINGS

The following publications include motor carrier, water carrier, broker, and freight forwarder transfer applications filed under Section 212(b), 206(a), 211, 312(b), and 410(g) of the Interstate Commerce Act.

Each application (except as otherwise specifically noted) contains a statement by applicants that there will be no significant effect on the quality of the human environment resulting from approval of the application.

Protests against approval of the application, which may include a request for oral hearing, must be filed with the Commission within 30 days after the date of this publication. Failure seasonably to file a protest will be construed as a waiver of opposition and in participation in the proceeding.

A protest must be served upon applicant's representative(s), or applicants (if no such representative is named), and the protestant must certify that such service has been made.

Unless otherwise specified, the signed original and six copies of the protest shall be filed with the Commission. All protests must specify with particularity the factual basis and the section of the Act or applicable rule governing the proposed transfer which protestant believes would preclude approval of the application. If the protest contains a request for oral hearing, the request shall be supported by an explanation as to why the evidence sought to be presented cannot reasonably be submitted through the use of affidavits.

The operating rights set forth below are in synopses form, but are deemed sufficient to place interested persons on notice of the proposed transfer.

No. MC-FC-76110, filed August 19, 1976, Transferor: DAVID ALEXANDER CARSON, 1306 Speaker Drive, Auburndale, Florida 33823; Transferor: Gloston Motor Lines, Inc., P.O. Box 1328, Lexington, North Carolina 27292. Applicant's Attorney: John P. M. Morehead, 401 North Broad Street, Suite 1800, Columbus, Ohio 43215. Authority sought for purchase by transferee of a portion of the operating rights of transferor, as set forth in Certificate of Registration No. MC 41555 (Sub-No. 64), issued October 10, 1966, as follows: specified commodities, from, to and between specified points in Massachusetts, Florida, Georgia, Louisiana, North Carolina, South Carolina, Tennessee, Virginia, Alabama, Mississippi, New York, New Jersey, Virginia, Rhode Island, Delaware, Pennsylvania, Maryland, Connecticut, Maine, New Hampshire, Vermont, West Virginia and Washington, D.C. Transferee presently holds no authority from this Commission. Application has not been filed for temporary authority under Section 210a(b).

No. MC-FC-76111, filed August 19, 1976, Transferor: ERNEST L. SEC-COMB, JR. AND ERNEST M. KINGS-BURY, a partnership, doing business as Kito's Transfer and Storage, 540 Front Street, Butte, Montana 59701. Transferor: Ernest L. Seccomb and Ernest M. Kingsbury, a partnership, doing business as Kito's Transfer & Storage, 700 East Front Street, Suite, Montana 59701. Authority sought for purchase by transferee of the operating rights of transferor, as set forth in Certificates No. MC 70176 and No. MC 70176 (Sub-No. 3), issued August 2, 1967 and February 16, 1971, respectively, as follows: Heavy machinery, between points in Silver Bow County, Mont., on the one hand, and, on the other, other points in Montana within 100 miles of Butte, Mont., equipment, materials and supplies, used or useful in the control of forest fires, between Butte, Mont., and points within 250 miles of Butte, general commodities, between Butte, Mont., on the one hand, and, on the other, points in Silver Bow County, Mont., and general commodities, with certain exceptions, between points in Silver Bow County, Mont., other than Butte, Mont.; and used household goods.
between specified counties in Montana. Transferee presently holds no authority from this Commission. Application has not been filed for temporary authority under Section 210(a)(b).

H. G. Homme, Jr.,
Secretary.

Office of Proceedings

MOTOR CARRIER TEMPORARY AUTHORITY APPLICATIONS

SEPTEMBER 2, 1976.

Important Notice: The following are notices of filing of applications for temporary authority under Section 210(a) of the Interstate Commerce Act provided for under the provisions of 49 CFR 1131.5. These rules provide that an original and six (6) copies of protests to an application may be filed with the field official named in the Federal Register publication no later than the 15th calendar day after the date of publication. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Food, produce and food items in bulk, in tank vehicles, from the plants and/or warehouse facilities of The Clorox Company and/or of the Grocery Store Products Company, located in Kentuck Square and West Chester, Pa., to points in Illinois, Indiana, Kansas, Michigan, Missouri, Ohio and Wisconsin, for 180 days. Supporting shipper: The Clorox Company, 1221 Broadway, Oakland, Calif. 94612. Send protests to: Keith D. Warner, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 513 Federal Office Bldg., 234 Summit St., Toledo, Ohio 43604.

No. MC 113988 (Sub-No. 387TA), filed August 25, 1976. Applicant: ERICKSON TRANSPORT CORP., 2105 E. Dale St., P.O. Box 3150 G.S.S., Springfield, Mo. Appellants' representative: H. G. Homme (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Bread crumbs, or cubes, salad dressing preparations, dry and mixed, dips, dry, (except in bulk), frozen, fruits, vegetables and storage facilities of The Clorox Company and/or of the Grocery Store Products Company, located in Kentuck Square and West Chester, Pa., to points in Illinois, Indiana, Kansas, Michigan, Missouri, Ohio and Wisconsin, for 180 days. Supporting shipper: The Clorox Company, 1221 Broadway, Oakland, Calif. 94612. Send protests to: Keith D. Warner, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 513 Federal Office Bldg., 234 Summit St., Toledo, Ohio 43604.

No. MC 114045 (Sub-No. 447TA), filed August 25, 1976. Applicant: TRANSCOLD EXPRESS, INC., P. O. Box 61228, D/FV Airport, Tex. 77561. Applicant's representative: J. B. Stuart (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Food, food products and food items in bulk, in tank vehicles, from the plants and/or warehouse facilities of Archer Daniels Midland Company, located in Decatur, Ill., to points in Arkansas, Louisiana, Oklahoma and New Mexico, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Archer Daniels Midland Company, P. O. Box 1470, Decatur, Ill. 62526. Send protests to: Opal M. Jones, Transportation Assistant, Interstate Commerce Commission, 1160 Commerce St., Room 1912, Dallas, Tex. 75242.

No. MC 110925 (Sub-No. 1147TA), filed August 25, 1976. Applicant: CHEMICAL LEAMAN TANK LINES, INC., 520 E. Lancaster Ave., P. O. Box 200, Downingtown, Pa. 19335. Applicant's representative: J. O'Brule (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Liquid chemicals, in bulk, in tank vehicles, from the plants of Malesco Chemical Co., at Sugarland, Tex., to points in Courtland and Decatur, Ala.; Miami, Ariz.; Armored and El Dorado, Ark.; Dania and Fort Lauderdale, Fla.; Dry Branch and White City, Ga.; Muncie and Whiting, Ind.; Tyrone, N. Mex.; and Ahsokle and Nixon, N.C., and to points in Illinois, Kansas, Louisiana, Mississippi, Missouri, Ohio, Minnesota, Kentucky and Wyoming, for 180 days. Supporting shipper: Malesco Chemical Company, 2901 Butterfield Road, Oak Brook, Ill. Send protests to: Monna A. Blodgett, Transportation Assistant, Interstate Commerce Commission, 600 Arch St., Room 3238, Philadelphia, Pa. 19106.

No. MC 110593 (Sub-No. 185TA), filed August 26, 1976. Applicant: COLDWAY FOOD EXPRESS, INC., P. O. Box 747, 113 N. Ohio Ave., Ohio Bldg., Sidney, Ohio 45365. Applicant's representative: John L. Maurer (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Bread crumbs, or cubes, salad dressing preparations, dry and mixed, dips, dry, (except in bulk), frozen, fruits, vegetables and storage facilities of The Clorox Company and/or of the Grocery Store Products Company, located in Kentuck Square and West Chester, Pa., to points in Illinois, Indiana, Kansas, Michigan, Missouri, Ohio and Wisconsin, for 180 days. Supporting shipper: The Clorox Company, 1221 Broadway, Oakland, Calif. 94612. Send protests to: Keith D. Warner, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 513 Federal Office Bldg., 234 Summit St., Toledo, Ohio 43604.

No. MC 115094 (Sub-No. 397TA), filed August 27, 1976. Applicant: COLDWAY FOOD EXPRESS, INC., P. O. Box 747, 113 N. Ohio Ave., Ohio Bldg., Sidney, Ohio 45365. Applicant's representative: Victor J. Tambascia (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Foodstuffs, in vehicles equipped with refrigerator or insulated equipment (except in bulk), in tank vehicles, from the plants and/or warehouse facilities of Krafco Corporation, at Champaign, Ill., to points in Maine, New Hampshire, Vermont, New York, New Jersey, Rhode Island, Connecticut, Pennsylvania, New Jersey, Delaware, Virginia, Maryland, and the District of Columbia. Restriction: Restricted to the transportation of traffic originating at the origin point and destined to the named destination points, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Krafco Corporation, 500 Peabody Court, Chicago, Ill. 60650. Send protests to: Keith D. Warner, District Supervisor, Bureau of Operations, 513 Federal Office Bldg., 234 Summit St., Toledo, Ohio 43604.

No. MC 115094 (Sub-No. 397TA), filed August 27, 1976. Applicant: GROVER TRUCKING CO., 1710 West Broadway, Idaho Falls, Idaho. Applicant's representative: Gene W. Bigler, 3207 31st Street South, Salt Lake City, Utah 84111. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Mineral fiber, miscellaneous products and insulating materials, from Pueblo, Colo., to points in Idaho, for 180 days. Supporting shipper: Intermountain Gas Company, P. O. Box 1906, H. R. E., Idaho 83229. Send protests to: Barney L. Hardin, District Supervisor, Interstate Commerce Commission, 550 West Fort, Box 07, Boise, Idaho 83724.

Canada. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting sand, in bulk, in tank vehicles, from McConnelsville, N.Y., to the International Boundary Line between the United States and Canada near Adrian Bay, N.Y., restricted to the transportation of traffic destined to points in the Province of Quebec, for 90 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporter: W. E. Cuthbert Ltd., 47 Duke St., Montreal, P.Q., Canada. Send protests to: David Demers, District Supervisor, 87 Stlat St., F.O. Box 548, Montpelier, Vt. 05602.

No. MC 123255 (Sub-No. 78TA), filed August 26, 1976. Applicant: B & L MOTOR FREIGHT, INC., 140 Everett Ave., Newark, Ohio 43055. Applicant’s representative: C. F. Schnee, Jr. (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Glass containers, from Clifton, N.J., to points in New York, for 180 days. Supporting carrier: Midland Glass Company, Inc., F.O. Box 557, Clifton, N.J. 07012. Send protests to: Frank L. Calvary, District Supervisor, Interstate Commerce Commission, 220 Federal Bldg., and U.S. Courthouse, 65 Marconi Blvd., Columbus, Ohio 43215.

No. MC 123255 (Sub-No. 77TA), filed August 26, 1976. Applicant: B & L MOTOR FREIGHT, INC., 140 Everett Ave., Newark, Ohio 43055. Applicant’s representative: C. F. Schnee, Jr. (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Container and container ends, from the warehouse site of the National Can Corporation, at Sharonville, Ohio, to Las Vegas, N.V., and Evansville, Ind., for 180 days. Supporting carrier: National Can Corporation, 8101 West Higgins Rd., Chicago, Ill. 60631. Send protest to: Hugh H. Wilson Company, at Sunbury, Pa., 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporter: W. R. S. Cuthbert Co., Inc., P.O. Box 3238, Philadelphia, Pa. 19106.

No. MC 123796 (Sub-No. 36 TA), filed August 27, 1976. Applicant: GEORGE L. APPLEGATE, 229 Carverton Road, Trucksville, Pa. 18708. Applicant’s representative: John W. Farray, Box 626, 2207 Old Geisleyburg Road, Camp Hill, Pa. 17011. Applicant’s representative: Eugene M. Malkin, Suite 6193, 5 Two Penn Center Plaza, Philadelphia, Pa. 19152. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Hair curlers, shampoo, cream rinses, bobby pins, waterproof plastic caps, towels, brushes, nail files, scissors, notions and novelties, (except plastic capes, towels, brooms, nail files); and such other materials and supplies used in the manufacture of the commodities described above; and such merchandise as is dealt in by variety stores (excluding commodities in bulk), originating at the plantsite of Wilson Manufacturing Corporation, and Hugh H. Wilson Company, at Sunbury, Pa., and destined to the Province of Quebec, for 180 days. Authority has also filed an underlying ETA seeking up to 90 days of operating authority. Supporter: Wilson Manufacturing Corporation, 19505, 10675 Worlds Fair Dr., Houston, Texas 77031. Applicant: B. L. T. CORPORATION, 405 Third Ave., Brooklyn, N.Y. 11215. Applicant’s representative: Eugene M. Malkin, Suite 6193, 5 Two Penn Center Plaza, Philadelphia, Pa. 19106.


No. MC 134086 (Sub-No. 3 TA), filed August 26, 1976. Applicant: CLIFFORD M. SHEROCK, 940 Blaine St., Woodburn, Oreg. 97071. Applicant’s representative: Robert R. Halle, 400 Pacific Blvd., Portland, Oreg. 97224. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Lumbar, from points in Clark County, Oreg., to Portland, Oreg., and destined to Clark and Cowlitz Counties, Wash., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shippers: Avison Lumber Co., P.O. Box 957, Moses, Oreg. 97038; Brazel Food Products, Inc., P.O. Box 5, Molalla, Oreg. 97038. Send protests to: A. E. Odoms, District Supervisor, Bureau of Operations, Interstate Commerce Commission, 114 Mooney, Denver, Col., 80204.

No. MC 1343494 (Sub-No. 20 TA), filed August 26, 1976. Applicant: B. L. T. CORPORATION, 405 Third Ave., Brooklyn, N.Y. 11215. Applicant’s representative: Eugene M. Malkin, Suite 6193, 5 Two Penn Center Plaza, Philadelphia, Pa. 19106. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Fireworks; common carrier, by water and truck, between Harrison, Jersey City and Bloomfield, N.J.; and Tampa, Fla., on the one hand, and, on the other, Birmingham, Leeds, Tuscaloosa, Geneva, and Anniston, Mont., and between Utica and Utica, on the other, Birmingham, Leeds, Tuscaloosa, Geneva, and Anniston, Mont., and Utica, N.Y. 13503. Applicant’s representative: Eugene M. Malkin, Suite 6193, 5 Two Penn Center Plaza, Philadelphia, Pa. 19106.
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No. MC 135658 (Sub-No. 2 TA), filed August 27, 1976. Applicant: ROCK RIVER CARGAGE, INC., R.R. No. 3, P.O. Box 430, Rock Falls, Ill., 61071. Applicant's representative: Robert T. Lawley, 300 Relish Bldg., Spring- field, Ill., 62701. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Refractory materials and products (except in bulk), from the plant of Northbrook Steel and Wire Company, from Lake County, Ind., to Sterling, Ill., under a continuing contract with Northbrook Steel and Wire Company, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Northbrook Steel and Wire Company, Lanny J. Nunz, Chief Rate Analyst, 125 N. Lake Shore Dr., Chicago, Ill., 60611. Send protests to: Patricia A. Roscoe, Transportation-Assistant, Interstate Commerce Commission, 26 Federal Plaza, New York, N.Y., 10007.

No. MC 136220 (Sub-No. 36 TA), filed August 27, 1976. Applicant: ROY SULLIVAN, doing business as SULLIVAN TRUCKING CO., P.O. Box 2154, Ponca City, Okla., 74602. Applicant's representative: Thomas Armstrong, 419 North May Ave., Oklahoma City, Okla., 73112. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Agricultural products (in bulk and in dump vehicles), from the plant of Oklahoma Light and Power Company, to near Enid, Okla., and to points in Kansas City, Mo., and points in its Commercial Zone, and to points in Kansas City, Kansas, and Texas, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Oklahoma Light and Power Company, R.D. No. 1, Box 430, Enid, Okla., 73704. Send protests to: Patricia Roscoe, Transportation-Assistant, Interstate Commerce Commission, 26 Federal Plaza, New York, N.Y., 10007.

No. MC 139923 (Sub-No. 19 TA), filed August 24, 1976. Applicant: MILLER TRUCKING CO., 105 S. 8th St., Stroud, Okla., 74079. Applicant's representative: Wilburn L. Williamson, 200 National Foundation Life Bldg., 3535 NW, 58th St., Oklahoma City, Okla., 73112. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Food, food products and food ingredients, in mechanically refrigerated equipment (except in bulk), from the plant and warehouse facilities of Archer Daniels Midland Company, at or near Decatur, Ill., to points in Arkansas, Louisiana, New Mexico, Oklahoma, and Texas, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Archer Daniels Midland Company, P.O. Box 1470, Decatur, Ill., 62525. Send protests to: J. Greene O.A., Benton, Ark., 72015. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Continental Express Company, P.O. Box 728, R.D. No. 2, Box 430, Rock Falls, Ill., 61071. Send protests to: Patricia A. Roscoe, Transportation-Assistant, Interstate Commerce Commission, 26 Federal Plaza, New York, N.Y., 10007.

No. MC 139923 (Sub-No. 21 TA), filed August 26, 1976. Applicant: MILLER TRUCKING CO., INC., 105 S. 8th St., Stroud, Okla., 74079. Applicant's representative: Jack H. Blanshan, Suite 200, 205 West Touhy Ave., Park Ridge, Ill., 60693. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Food, food products, fruit juices and table sauces (except commodities in bulk), from the plant and warehouse facilities of or railroad depots, in Howard, Iowa, to locations at or near Kenosha, Wis., and North Chicago, Ill., to Kansas City, Mo., and points in its Commercial Zone, and to points in Kansas City, Kansas, and Texas, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Ocean Spray Cranberry Company, Inc., 150 Industrial Dr., Worcester, Mass., 01605. Send protests to: J. Greene O.A., Benton, Ark., 72015. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Ocean Spray Cranberry Company, Inc., 150 Industrial Dr., Worcester, Mass., 01605. Send protests to: J. Greene O.A., Benton, Ark., 72015.

No. MC 142380TA, filed August 26, 1976. Applicant: GABIT, INC., 35 Brown St., Washington, D.C., 20582. Applicant's representative: Richard E. Fagan, P.O. Box 921, Highland Park, N.J., 08904. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: (1) products of Loma Linda, Calif., to points in Connecticut, Kentucky, Maryland, Massachusetts, New York, Ohio, Pennsylvania, Tennessee, Virginia, Washington, D.C., and West Virginia, and (2) Talc, materials and supplies used in the manufacturing or ceramics (except in bulk), from the above destination states to Stillman, N.J., under a continuing contract with Stillman, N.J. Send protests to: Joel Morrows, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 9 Clinton St., Room 618, Newark, N.J., 07102.

No. MC 142381TA, filed August 26, 1976. Applicant: WAYNE E. BELL, doing business as WAYNE BELL, Box 34,
NOTICES

Motor Carriers of Property

No. MC 56679 (Sub-No. 88TA), filed August 26, 1976. Applicant: BROWN TRANSPORT CORP., 123 Milton Ave., SE., Atlanta, Ga. 30315. Applicant's representative: R. J. Reynolds, III, 1400 Peachtree Bldg., Atlanta, Ga. 30308. Authority sought to operate as a common carrier, by motor vehicle, over regular routes, transporting: General commodities described as applicant's products, as defined by the Commission in the application. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Dry animal and poultry feed, dry animal and poultry mineral mixtures, animal and poultry tonics, insecticides (other than agricultural), fertilizers, dry and liquid animal and poultry feed, and feed ingredients.

No. MC 56376 (Sub-No. 13TA), filed August 26, 1976. Applicant: MEINK EMERSON TRUCKING, INC., Route No. 1, Oakwood, Ill. 60668. Applicant's representative: Robert T. Lavery, 300 Relish Bldg., Springfield, Ill. 62701. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Dry animal and poultry feed, dry animal and poultry mineral mixtures, animal and poultry tonics, insecticides (other than agricultural), fertilizers, dry and liquid animal and poultry feed, and feed ingredients.

No. MC 108430 (Sub-No. 760TA), filed August 27, 1976. Applicant: QUALITY CALIFORNIA FEEDS, INC., Box 186, Pleasant Prairie, Wis. 53155. Applicant's representative: Joseph K. Reber (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Feed, feed ingredients, and advertising matter relating to such products.

No. MC 119619 (Sub-No. 697TA), filed August 27, 1976. Applicant: DISTRIBUTORS SERVICE CO., 3000 W. 43rd St., Chicago, Ill. 60638. Applicant's representative: Bruce D. Johnson, Jane City Plaza, Flushing, N.Y. 11369. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Meat, meat by-products, and meat by-products distributed by meat packers, as described in Sections A and C of Appendix I to the report in Descriptions in Motor Carrier Operations, 122 F.R. 7518 and 768 (except hides and commodities in bulk), from the plantsite and storage facilities of Elcoma Foods, Inc., located at Elkhart, Ind., to points in Connecticut, Delaware, Illinois, Iowa, Kansas, Ken-
tucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, Wisconsin, and Iowa. The common carrier may seek to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Clay, clay products, related articles, fitting and jointing materials, from Pittsburg, Kansas, to points in Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nevada, New Mexico, Ohio, Oklahoma, South Dakota, Tennessee, Texas, Wisconsin, and Wyoming; and (2) clay, clay products, fittings, equipment, materials, and supplies, used or to be used in packaging, transporting, and distributing of clay products and jointing materials, from the plantsites and/or storage facilities of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo., to the plantsite and/or storage facility of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo.

Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Miller Brewer Company, 3825 Beech Ave., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Richard G. McCurdy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (2) Foodstuffs, alcoholic beverages, commodities in bulk, which because of size or weight require the use of special equipment, from Muskogee and Greenville, Mich.; Brockway, Pa.; Corning, N.Y.; Cumberland, Md.; and Jackson, Miss., to points in Idaho, Washington, Oregon, California, Nevada, Arizona and Utah and from Memphis, Tenn., to points in Nevada, for 180 days. Supporting shipper: Miller Brewer Company, 3825 Beech Ave., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Richard G. McCurdy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (2) Clay, clay products, related articles, fitting and jointing materials, from Pittsburg, Kansas, to points in Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nevada, New Mexico, Ohio, Oklahoma, South Dakota, Tennessee, Texas, Wisconsin, and Wyoming; and (2) clay, clay products, fittings, equipment, materials, and supplies, used or to be used in packaging, transporting, and distributing of clay products and jointing materials, from the plantsites and/or storage facilities of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo., to the plantsite and/or storage facility of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo.

Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Miller Brewer Company, 3825 Beech Ave., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Richard G. McCurdy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (2) Foodstuffs, alcoholic beverages, commodities in bulk, which because of size or weight require the use of special equipment, from Muskogee and Greenville, Mich.; Brockway, Pa.; Corning, N.Y.; Cumberland, Md.; and Jackson, Miss., to points in Idaho, Washington, Oregon, California, Nevada, Arizona and Utah and from Memphis, Tenn., to points in Nevada, for 180 days. Supporting shipper: Miller Brewer Company, 3825 Beech Ave., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Richard G. McCurdy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (2) Clay, clay products, related articles, fitting and jointing materials, from Pittsburg, Kansas, to points in Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nevada, New Mexico, Ohio, Oklahoma, South Dakota, Tennessee, Texas, Wisconsin, and Wyoming; and (2) clay, clay products, fittings, equipment, materials, and supplies, used or to be used in packaging, transporting, and distributing of clay products and jointing materials, from the plantsites and/or storage facilities of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo., to the plantsite and/or storage facility of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo.

Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Miller Brewer Company, 3825 Beech Ave., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Richard G. McCurdy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (2) Foodstuffs, alcoholic beverages, commodities in bulk, which because of size or weight require the use of special equipment, from Muskogee and Greenville, Mich.; Brockway, Pa.; Corning, N.Y.; Cumberland, Md.; and Jackson, Miss., to points in Idaho, Washington, Oregon, California, Nevada, Arizona and Utah and from Memphis, Tenn., to points in Nevada, for 180 days. Supporting shipper: Miller Brewer Company, 3825 Beech Ave., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Richard G. McCurdy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (2) Clay, clay products, related articles, fitting and jointing materials, from Pittsburg, Kansas, to points in Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nevada, New Mexico, Ohio, Oklahoma, South Dakota, Tennessee, Texas, Wisconsin, and Wyoming; and (2) clay, clay products, fittings, equipment, materials, and supplies, used or to be used in packaging, transporting, and distributing of clay products and jointing materials, from the plantsites and/or storage facilities of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo., to the plantsite and/or storage facility of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bexar, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo.
NOTICES

[Notice No. MC-C-4000 (Sub-No. 6)]

MOTOR TRANSPORTATION OF PASSENGERS INCIDENTAL TO TRANSPORTATION BY AIRCRAFT

Chicago O’Hare Airport Terminal Area;
Petition to Extend Exempt Zone

Petitioner: Hammond Yellow and Checker Cab, Inc., doing business as Airline Limousine Service, Hammond, Ind., Petitioner’s representative: Donald W. Smith, Suite 2465, One Indiana Square, Indianapolis, Ind. 46204. By the instant petition, filed May 17, 1976, the above named petitioner requests the Commission to reopen the proceeding in MC-C-4000, 95 M.C.C. 535 at pages 538-539, for the purpose of redefining the limits of the zone within which may be performed motor transportation of passengers having an immediately prior or subsequent movement by air, pursuant to section 203(b)(7a) of the Interstate Commerce Act, within the Chicago O’Hare International Airport air terminal area so as to include all points in Lake and Porter Counties, Ind. The terminal areas at airports within which such transportation may be performed under the section 203(b)(7a) exemption were redefined on July 17, 1964, in Motor Transportation of Passengers Incidental to Transportation by Aircraft, 95 M.C.C. 526, at pages 538-539 (49 CFR 1047.45). Petitioner here seeks to have the exemption redefined to include all points in Lake and Porter Counties, Ind.

Petitioner states that it has been conducting passenger terminal operations for a number of years but has found that not only are numerous passengers utilizing the Chicago O’Hare facilities for transportation do, in fact, originate at various points in Lake and Porter Counties which are beyond the exempt area.

No oral hearing is contemplated at this time but any interested person wishing to make representations in favor of or in opposition to the relief sought by the petitioner may do so by submitting written statements. All such persons, including motor carriers, air carriers, shippers and receivers of freight, and others, whether or not subject to the Commission’s jurisdiction, are invited to submit representations setting forth any facts or argument pertinent to the proper scope of the exempt zone surrounding the O’Hare International Airport at Chicago, Ill. An original and 15 copies, where possible, of representations containing data, views, or arguments shall be filed with the Commission on or before November 8, 1976. One copy of each representation should be served upon petitioner’s representative shown above.

Written material or suggestions submitted will be available for public inspection at the Office of the Secretary of the Interstate Commerce Commission, 12th & Constitution, Washington, D.C., during regular business hours.

Notice to the general public of the matter herein under consideration will be given by publication in a copy of this notice in The Federal Register and by filing a copy thereof with the Director, Office of the Federal Register.

By the Commission.

H. Gonoor Homr, Jr.,
Acting Secretary.

[FR Doc.76-25900 Filed 9-8-76;8:45 am]

[Volume No. 47]

SEPTEMBER 3, 1976.

Permanent authority petitions and applications: finance matters (including temporary authorities); railroad abandonments; alternate route deviation letters; and intrastate applications concurrently seeking authority on interstate or foreign commerce.

PETITIONS FOR MODIFICATION, INTERPRETATION OR RESTATEMENT OF OPERATING RIGHTS AUTHORITY

The following petitions seek modification or interpretation of existing operating rights authority, or reinstatement of terminated operating rights authority.

An original and one copy of protests to the granting of the requested authority must be filed with the Commission on or before October 13, 1976. Such protest shall comply with Special Rule 247(d) of the Commission’s General Rules of Practice (49 CFR 1047.247) and shall include a concise statement of protestant’s interest in the proceeding and copies of pertinent facts and conflicting authorities. Verified statements in opposition should not be tendered at this time. A copy of the protest shall be served concurrently upon petitioner’s representative, or petitioner if no representative is named.

No. MC 121630 (Sub-No. 3) (Notice of Filing of Petition to Remove Restrictions), filed May 17, 1976. Petitioner: LEMORE TRANSPORTATION, INC., doing business as: ROYAL TRUCKING CO., 1420 Royal Industrial Way, P.O. Box 6966, Concord, Calif. 94524. Petitioner’s representative: Raymond A. Grecco, Jr., 100 Pine St., Suite 2550, San Francisco, Calif. 94111. Petitioner holds a motor common carrier certificate in No. MC 121630 (Sub-No. 3). Issued July 20, 1970, authorizing transportation over irregular routes, of (1) Dry commodities, in bulk, in dump or hopper-type vehicles (except earth, sand, loam, gravel, stone, cement, asphalt, and cement or asphalt mixtures), between points in Solano, Contra Costa and Alameda Counties, Calif., on the one hand, and, on the other, Pitts-

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burg, Benicia, Selby, Richmond, Oakland, and Alameda, Calif.; and (2) General commodities (except (a) commodities of unusual value, (b) classes A and B explosives, (c) household goods as defined by the Commission, (d) commodities requiring special equipment, (e) commodities in vehicles equipped with mechanical refrigeration, (f) compressed gases, (g) commodities in semi-solid form, and commodities in suspension in liquids, in bulk, in tank vehicles, (h) dry ice, (i) fresh fruits and vegetables), between points in San Francisco, Alameda, and Contra Costa County, Calif., which are on and east of California Highway 82, those points in Santa Clara County, Calif., which are on and north of California Highway 82, and those points in Solano County, Calif., which are bounded by a line beginning at the junction of Interstate Highway 680 and the Solano-Contra Costa County line, extending along Interstate Highway 680 to junction of Interstate Highway 80, thence extending along Interstate Highway 80 to junction of the Solano-Contra Costa County line, and thence extending along the Solano-Contra Costa, Calif., County line to the point of beginning (i.e., the junction of said county line and Interstate Highway). The petition sets out all the necessary facts and relevant authorities, and requests that the application be granted.

By the instant petition, petitioner seeks to delete the restriction from the above authority.


By the instant petition, petitioner seeks to delete the restriction from the above authority.

Motor Carrier, Broker, Water Carrier and Freight Forwarder - Operating Rights Applications: The following applications are governed by Special Rule 247 of the Commission's General Rules of Practice (49 CFR §1100.247). These rules provide, among other things, that a protest to the granting of an application must be filed with the Commission within 30 days after the date of notice of filing of the application is published in the Federal Register.

For a protest to be considered timely under these rules, it must contain a statement of protest and a statement of protest in detail, whether by joinder, interline, or other means, by which protestant would use such authority to provide all or part of the service proposed, and shall specify with particularity the facts, matters, and things relied up. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Paper, paper articles, paperboard and paperboard articles (except commodities in bulk), from Chicago and Lynchburg, Va., to points in Connecticut, D.C., Kentucky, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, South Carolina, Vermont, Virginia, West Virginia, and the District of Columbia.

Note.—For a protest to be considered timely under these rules, it must contain a statement of protest and a statement of protest in detail, whether by joinder, interline, or other means, by which protestant would use such authority to provide all or part of the service proposed, and shall specify with particularity the facts, matters, and things relied up.

No. MC 6535 (Sub-No. 58), filed August 3, 1976. Applicant: GEORGE TRANSFER AND RIGGING COMPANY, INCORPORATED, P.O. Box 931, Fairmont, Md. 21102. Applicant's representative: John Guadano, 1000 16th St., N.W., Washington, D.C. 20005. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: General commodities, in bulk, in tank vehicles, paper, paper articles, paperboard and paperboard articles; (except commodities in bulk), from Chicago and Lynchburg, Va., to points in Connecticut, D.C., Kentucky, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, South Carolina, Vermont, Virginia, West Virginia, and the District of Columbia.

Note.—Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: General commodities, in bulk, in tank vehicles, paper, paper articles, paperboard and paperboard articles; (except commodities in bulk), from Chicago and Lynchburg, Va., to points in Connecticut, D.C., Kentucky, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, South Carolina, Vermont, Virginia, West Virginia, and the District of Columbia.


Note.—For a protest to be considered timely under these rules, it must contain a statement of protest and a statement of protest in detail, whether by joinder, interline, or other means, by which protestant would use such authority to provide all or part of the service proposed, and shall specify with particularity the facts, matters, and things relied up.

No. MC 2195 (Sub-No. 169), filed August 2, 1976. Applicant: DAN DUGAN TRANSPORT COMPANY, 41st & Grange Avenue, Sioux Falls, S. Dak. 57105. Applicant's representative: John Dugan (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Anhydrous ammonia, in bulk, in tank vehicles, from the storage facilities of Farnall Industries, Inc., located at or near Earnslee and Benson, Minn., to points in Minnesota, Montana, North Dakota, South Dakota and Wisconsin.

Note.—For a protest to be considered timely under these rules, it must contain a statement of protest and a statement of protest in detail, whether by joinder, interline, or other means, by which protestant would use such authority to provide all or part of the service proposed, and shall specify with particularity the facts, matters, and things relied up.
NOTICE

No. 57897 (Sub-No. 2), filed July 30, 1976. Applicant: LESTER SMITH TRUCKING, INC., 11440 West 44th Avenue, West Ridge, Colo. 80033. Applicant's representative: David J. Listler, P.O. Box 1136, Arvada, Colo. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Construction equipment, farm machinery and used farm equipment, between points in Colorado, Iowa, Kansas, Missouri, Nebraska, and Wyoming.

No. 61231 (Sub-No. 94), filed August 2, 1976. Applicant: ACE LINES, INC., 4143 East 63rd St., Des Moines, Iowa 50317. Applicant's representative: William L. Fairchild, 1180 Financial Center, Des Moines, Iowa 50309. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Concrete, pipes, and couplings, connectors and accessories for pipe (except iron or steel pipe), from the plant site of Armo Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas, Missouri, and Nebraska.

No. 61596 (Sub-No. 319), filed August 2, 1976. Applicant: HERMAN BROS. TRUCKING INC., 2563 St. Marys Avenue, P.O. Box 189, Omaha, Neb. 68101. Applicant's representative: John E. Smith, (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Anhydrous ammonia, in bulk, in tank vehicles, from the storage facilities of Farmland Industries located at or near Fremont, Neb., to points in Kansas, Missouri, Oklahoma, Nebraska, and Wisconsin.

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No. 57897 (Sub-No. 2), filed July 30, 1976. Applicant: LESTER SMITH TRUCKING, INC., 11440 West 44th Avenue, West Ridge, Colo. 80033. Applicant's representative: David J. Listler, P.O. Box 1136, Arvada, Colo. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Construction equipment, farm machinery and used farm equipment, between points in Colorado, Iowa, Kansas, Missouri, Nebraska, and Wyoming.

No. 61231 (Sub-No. 94), filed August 2, 1976. Applicant: ACE LINES, INC., 4143 East 63rd St., Des Moines, Iowa 50317. Applicant's representative: William L. Fairchild, 1180 Financial Center, Des Moines, Iowa 50309. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Concrete, pipes, and couplings, connectors and accessories for pipe (except iron or steel pipe), from the plant site of Armo Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas, Missouri, and Nebraska.

No. 61596 (Sub-No. 319), filed August 2, 1976. Applicant: HERMAN BROS. TRUCKING INC., 2563 St. Marys Avenue, P.O. Box 189, Omaha, Neb. 68101. Applicant's representative: John E. Smith, (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Anhydrous ammonia, in bulk, in tank vehicles, from the storage facilities of Farmland Industries located at or near Fremont, Neb., to points in Kansas, Missouri, Oklahoma, Nebraska, and Wisconsin.

No. 57897 (Sub-No. 2), filed July 30, 1976. Applicant: LESTER SMITH TRUCKING, INC., 11440 West 44th Avenue, West Ridge, Colo. 80033. Applicant's representative: David J. Listler, P.O. Box 1136, Arvada, Colo. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Construction equipment, farm machinery and used farm equipment, between points in Colorado, Iowa, Kansas, Missouri, Nebraska, and Wyoming.

No. 61231 (Sub-No. 94), filed August 2, 1976. Applicant: ACE LINES, INC., 4143 East 63rd St., Des Moines, Iowa 50317. Applicant's representative: William L. Fairchild, 1180 Financial Center, Des Moines, Iowa 50309. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Concrete, pipes, and couplings, connectors and accessories for pipe (except iron or steel pipe), from the plant site of Armo Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas, Missouri, and Nebraska.

No. 61596 (Sub-No. 319), filed August 2, 1976. Applicant: HERMAN BROS. TRUCKING INC., 2563 St. Marys Avenue, P.O. Box 189, Omaha, Neb. 68101. Applicant's representative: John E. Smith, (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Anhydrous ammonia, in bulk, in tank vehicles, from the storage facilities of Farmland Industries located at or near Fremont, Neb., to points in Kansas, Missouri, Oklahoma, Nebraska, and Wisconsin.
No.-If a hearing is deemed necessary, the applicant requests it be held at Richmond, Va., or Washington, D.C.

No. MC 80430 (Sub-No. 153), filed July 27, 1976. Applicant: GATEWAY TRANS-PORTATION, INC., 145 Paul Drive, La Crosse, Wis. 54601. Applicant's representative: Drew L. Carraway, 501 Perpetual Bldg., 111 E Street, NW., Washington, D.C. 20004. Authority sought to operate as a common carrier, by motor vehicle, over regular routes, transporting: General commodities (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk, and those requiring special equipment), (1) Between Iuka, Miss., and Memphis, Tenn. serving all intermediate points on U.S. Highway 72, from Iuka to junction Mississippi Highway 15; (2) Between Columbus, Miss., and Corinth, Miss., serving all intermediate points: (a) From Columbus over U.S. Highway 45 to Corinth, Miss., and return over the same route; and (b) Over U.S. Highway 82 to junction U.S. Highway Alternate 45, thence over U.S. Highway Alternate 45 to junction U.S. Highway 45 and return over the same route: (3) Between Columbus via Brownfield, Miss., serving all intermediate points:

From Columbus, Miss., over U.S. Highway 82 to junction Mississippi Highway 15, thence via Mississippi Highway 15 to Brownfield, Miss., and return over the same route; (4) Between Columbus, Miss., and Iuka, Miss., serving all intermediate points: From Columbus, Miss., over U.S. Highway 45 to junction Mississippi Highway 26 to Iuka, Miss., and return over the same route; (5) Between junction Mississippi Highway 15 with Mississippi Highway 32, and junction Mississippi Highway 32 with U.S. Highway Alternate 45 serving all intermediate points: From junction Mississippi Highway 15 and Mississippi Highway 32, thence over Mississippi Highway 32 to junction Mississippi Highway 32 and U.S. Highway Alternate 45, and return over the same route; and (6) Between Trenton, Mo., and Atlanta, Ga., serving no intermediate points: From Trenton, Mo., over U.S. Highway 78 to junction U.S. Highway 278 via Hamilton, Ala., thence over U.S. Highway 278 to junction Alabama Highway 5 via Natural Bridge, Ala., thence over Alabama Highway 5 to junction U.S. Highway 78 via Jasper, Ala., thence over U.S. Highway 78 to Atlanta, Ga., and return over the same route serving all points of Mississippi overbounded on the east by the Mississippi-Alabama State line, on the north by the Mississippi-Tennessee State line, on the west by Mississippi Highway 15, and on the south by U.S. Highway 82, including points on the indicated portions of Mississippi Highway 15 and U.S. Highway 82, as off route points in connection with applicant's regular route operations requested above.

No.-If a hearing is deemed necessary, the applicant requests it be held at Tupelo, Miss. and Orlando, Fla.

No. MC 82492 (Sub-No. 135), filed July 30, 1976. Applicant: MICHIGAN & NEBRASKA TRANS CO., Inc., P.O. Box 2855, 2109 Omahn 543, Lincoln, Neb. 68503. Applicant's representative: William C. Harris (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Petroleum products, in containers, from Karna.s City, Pa., to points in Michigan.

No.-If a hearing is deemed necessary, the applicant requests it be held at Wash-ington, D.C.


Mo. MC 82841 (Sub-No. 182), filed Aug. 2, 1976. Applicant: PORTATION, INC., 1077 "T" St., Omaha, Nebr. 68127. Applicant's representative: Donald L. Stern, 530 Uninc Bldg., 7100 West Center Rd., Omaha, Nebr. 68106. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Lead and alloys, from Omaha, Nebr., to points in the United States (except Alaska and Hawaii); (2) materials and supplies (except in bulk) used in the manufacture and distribution of lead alloys, from points in the United States (except Alaska and Hawaii), to Omaha, Nebr.; and (3) Metals, Nebr. and Tacoma, Wash., to Amarillo, Tex., restricted in (1), (2), and (3) above to the transportation of shipments originating at or destined to the facilities of Armo Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas and Nebraska.

Mo. MC 94530 (Sub-No. 386), filed July 30, 1976. Applicant: TRANSIT HOMES, INC., F.O. Box 1628, Greenville, S.C. 29622. Applicant's representative: Anthony A. King, Jr. (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Trailers, designed to be drawn by passenger automobiles, in initial movements, and buildings in sections, mounted on wheeled undercarriages, from points in Columbia and Leon Counties, Fla., to points in Georgia, South Carolina, and Tennessee.

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No. MC 103501 (Sub-No. 376), filed August 4, 1976. Applicant: FLEET TRANSPORT COMPANY, INC., 934 44th Avenue, North, Nashville, Tenn. 37209. Applicant's representative: Russell E. Stone, F.O. Box 98058, Nashville, Tenn. 37209. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Ferrous sulfamate, from Effauf, Ala., to Dumbarton, S.C.

No. MC 103501 (Sub-No. 377), filed Aug. 4, 1976. Applicant: FLEET TRANS-
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PORT COMPANY, INC., 934 44th Avenue, North, Nashville, Tenn. 37209. Applicant: Representative: Russell E. Stone, P.O. Box 90403, Nashville, Tenn. 37209. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Dry slag, in bulk, in tank or hopper type vehicles, from Carrollton, Ga., to Ozark, Ala.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Atlanta, Ga., or Wilton Junction, Iowa, to Norfolk, Nebr.
P.O. Box 90408, Nashville, Tenn.

No. MC 106195 (Sub-No. 9), filed July 28, 1976. Applicant: CLARK BROs. TRANSFER, INC., 600 North First St., P.O. Box 388, Norfolk, Nebr. 68701. Applicant’s representative: Michael J. Osborn, P.O. Box 82283, Lincoln, Nebr. 68501. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Iron and steel articles, as described in Descriptions in Motor Carrier Certificates, 61 M.C.C. 209 and 767, from Chicago, Alton and Sterling, Ill.; Kansas City and St. Louis, Mo.; and Wilson Junction, Iowa, to Norfolk, Nebr.; and E. O. & S. points in Ohio on and north of Interstate Highway 70, to Ill. Nucor Steel Mill located at or near Norfolk, Nebr.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Omaha, Neb.

No. MC 106308 (Sub-No. 746), filed August 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant’s representative: Irvin Tull (Same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Metal and nonmetal ingot, scrap metal, and (2) Steel flat and coil products, from points in the United States (except Alaska and Hawaii), to points in the United States (except Alaska and Hawaii).

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Little Rock, Ark.

No. MC 105099 (Sub-No. 747), filed August 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant’s representative: Irvin Tull (Same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Single wide and double wide mobile homes, in initial movements, in truckaway service, from Adams County, Colo., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Denver, Colo.

No. MC 106398 (Sub-No. 748), filed August 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant’s representative: Irvin Tull (Same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Mobile homes, in initial movements, in truckaway service, from point in Cincinnati and Montgomery Counties, Tenn., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Louisville, Ky.

No. MC 106398 (Sub-No. 751), filed Aug. 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant’s representative: Irvin Tull (Same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Mobile homes, irrespective of their intended use, in initial movements, in truckaway service, from points in Muscatine and White Counties, Ark., to points in the United States (except Alaska and Hawaii).

NOTE.—Dual operations and common control may be involved. If a hearing is deemed necessary, applicant requests it be held at Little Rock, Ark.

No. MC 106398 (Sub-No. 762), filed Aug. 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant’s representative: Irvin Tull (Same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Mobile homes, irrespective of their intended use, in initial movements, in truckaway service, from points in Franklin, Va., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control and dual operations may be involved. If a hearing is deemed necessary, applicant requests it be held at Charlotte, N.C.

No. MC 106453 (Sub-No. 10), filed Aug. 6, 1976. Applicant: ANTRIM TRANSPORTATION CO., INC., 7-11 Suffern Place, Suffern, N.Y. 10901. Applicant’s representative: John L. Alfano, 550 Mainmonce Avenue, Harrison, N.Y. 10528. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Glass containers, from the plants of Midland Glass Company, located at or near Chicago, Ill., to points in New York; and (2) returned shipments, from points in New York, to the origin point named in (1) above.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at New York.

No. MC 107575 (Sub-No. 41), filed July 29, 1976. Applicant: ATLAS TRUCK LINE, INC., 781 San Jacinto Bldg., P.O. Box 9546, Houston, Tex. 77005. Applicant’s representative: Thomas Harper, P.O. Box 43, Fort Smith, Ark. 72901. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Fencing, fence posts, fencing, wire and wood products; and (2) steel wire products, (a) from Van Buren, Ark., to points in Alabama, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Nebraska, Ohio, Oklahoma, Tennessee, Texas and Reno, Nev.; and (b) from Reno, Nev., to Van Buren, Ark.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Kansas City, Mo., or Washington, D.C.

No. MC 107403 (Sub-No. 923, filed Aug. 3, 1976. Applicant: MATLACK, INC., Ten West Baltimore Avenue, Lansdowne, Pa. 19050. Applicant’s representative: John Nelson (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Sulphur hexafluoride, in bulk, in shipper provided tank trailers, from Metropolis, Ill., to East Chicago, Ind.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 107466 (Sub-No. 1040), filed August 2, 1976. Applicant: RUAN TRANSPORT CORPORATION, 3200 Ruan Center, 666 Grand Avenue, Des Moines, Iowa 50309. Applicant’s representative: Albert E. Berkey, Box 856, Des Moines, Iowa 50304. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Natural latex, in bulk, in tank vehicles, from the facilities of Georgia Pacific Corporation located at or near Fort Dodge, Iowa, to points in Ohio.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Chicago, Ill. or Des Moines, Iowa.

No. MC 107515 (Sub-No. 1018), filed August 2, 1976. Applicant: REFRIGERATED TRANSPORT CO., INC., P.O. Box 308, Forest Park, Ga., 30092. Applicant’s representative: Alan E. Serby, 3379 Peachtree Road, N.E.; Suite 375, Atlanta, Ga. 30326. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Paper, paper articles and paper products, from the plants of the warehouse facilities of Union Camp Corporation, located at or near Franklin, Va., to points in Chicago, Ill., and the Special Zone; Indiana on and north of U.S. Highway 40; Michigan on and south of Michigan Highway 21, and points in Ohio.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 107544 (Sub-No. 127), filed August 2, 1976. Applicant: LEMMON TRANSPORT COMPANY, INCORPORATED, P.O. Box 800, Marion, Va. 24354. Applicant’s representative: Harry C. Ames, Jr., 666 Eleventh Street, N.W., Washington, D.C. 20001. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Natural latex, in bulk, in tank vehicles, from Charleston, S.C., to points in Alabama, Connecticut, Delaware, Florida, Georgia, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, New Hampshire, New Jersey, New York, North Carolina,

No. MC 107715 (Sub-No. 9), filed August 2, 1976. Applicant: DUQAL LTD., 3503 E. First St., Los Angeles, Calif. 90029. Applicant, Chicago, 111., and Meigs and Monroe Counties, Tenn., points in Iowa, Kansas, Mississippi, and the District of Columbia.

No. MC 107715 (Sub-No. 9), filed August 2, 1976. Applicant: J. W. WILLIS TRUCKING CO., 3608 Electra Lane, Dallas, Tex. 75220. Applicant's representative: James W. Hightower, 136 Wynnewood Professional Bldg., Dallas, Tex. 75224. Authority sought to be held at either Columbus, Ohio, or Dallas, Tex. If a hearing is deemed necessary, the applicant requests it be held at either Columbus, Ohio, or Roanoke, Va.

No. MC 107993 (Sub-No. 47), filed August 2, 1976. Applicant: J. J. WILLIS TRUCKING CO., 3608 Electra Lane, Dallas, Tex. 75220. Applicant's representative: James W. Hightower, 136 Wynnewood Professional Bldg., Dallas, Tex. 75224. Authority sought to operate as a common carrier, by motor vehicle, over regular routes, transporting: Potting soil and pesticides (except in bulk), and potting mix in mixed loads with feeds and fertilizers, from points in and south of Fresno, Inyo, Monterey and San Benito Counties, Calif., to points in Arizona, California, Colorado, Idaho, Montana, Nevada, Oregon, Utah, Washington, and the District of Columbia.

No. MC 109692 (Sub-No. 40), filed August 2, 1976. Applicant: GRAIN BELT TRANSPORTATION CO., INC., 340 North James, Kansas City, Kan. 66105. Applicant's representative: Tom E. Krebsinger, 910 Brookfield Bldg., 101 West Eleventh, Kansas City, Mo. 64105. Authority sought to operate as a common carrier, by motor vehicle, over regular routes, transporting: Pipe and pipe fittings, couplings, connectors, and accessories (except iron and steel pipe), from the plantsite and storage facilities of Cement Asbestos Products Company, located at or near Van Buren, Ark., to points in Arizona, California, Colorado, North Dakota and Utah.

No. MC 110144 (Sub-No. 18), filed July 30, 1976. Applicant: JACE E. ROBINSON, doing business as Robinson Paving Co., 9007 Paper Mill Road, P.O. Box 10234, Knoxville, Tenn. 37919. Applicant's representative: Warren A. Goff, 5100 Poplar Avenue, 200 Clark Tower, Memphis, Tenn. 38117. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: General commodities (except those of unusual value), Classes A and B explosives, commodities in bulk, household goods as defined by the Commission, and commodities requiring special handling, from Memphis, Tenn., and the District of Columbia.

No. MC 110645 (Sub-No. 131), filed August 2, 1976. Applicant: REDWIN CARRIERS, INC., P.O. Box 426, Tampa, Fla. 33601. Applicant's representative: J. V. McCoy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Sodium sulphate and sodium sulphite and mixtures thereof, dry, in bulk, in tank vessels, from Montgomery, Ala., to points in Alabama, Connecticut, Delaware, Illinois, (except the East St. Louis Commercial Zone), Indiana, Kentucky, Maine, Maryland, Massachusetts, Michigan, Missouri (except the St. Louis Commercial Zone), New Hampshire, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, and the District of Columbia, restricted to traffic originating at the plantsite and storage facilities of Reichhold Chemicals, Inc., at Montgomery, Ala., and destined to the destination territory described above.

No. MC 110479 (Sub-No. 142), filed August 2, 1976. Applicant: JONES TRUCK LINES, INC., 819 East Emma Avenue, Spring Branch, Ark. 72964. Applicant's representative: Don A. Smith, P.O. Box 43, Fort Smith, Ark. 72901. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Fencing, fencing materials, wire, and wire products, from Van Buren, Ark., to Reno, Nev., and points in California, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Mississippi, Missouri, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, South Dakota, Texas, Texas, Vermont, Virginia, West Virginia, Wisconsin, and the District of Columbia.


No. MC 111045 (Sub-No. 131), filed August 2, 1976. Applicant: REDWIN CARRIERS, INC., P.O. Box 426, Tampa, Fla. 33601. Applicant's representative: J. V. McCoy (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Sodium sulphate and sodium sulphite and mixtures thereof, dry, in bulk, in tank vessels, from Montgomery, Ala., to points in Alabama, Connecticut, Delaware, Illinois, (except the East St. Louis Commercial Zone), Indiana, Kentucky, Maine, Maryland, Massachusetts, Michigan, Missouri (except the St. Louis Commercial Zone), New Hampshire, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, and the District of Columbia, restricted to traffic originating at the plantsite and storage facilities of Reichhold Chemicals, Inc., at Montgomery, Ala., and destined to the destination territory described above.

No. MC 111729 (Sub-No. 673), filed August 3, 1976. Applicant: PUROLATOR COURIER CORP., 3333 New Hyde Park Road, New Hyde Park, N.Y. 11040. Applicant's representative: John M. Delany (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Liquid chemicals, in tank vehicles, from the facilities of Chemical Inter-Continentals, Incorporated, at or near Blythewood, Ark.; Depue, Marseilles, and Wood River, Ill.; Flint, Grand Rapids, Kalamazoo, Mt. Clemens, Port Huron and Warren, Mich.; and Louisiana, Mo.; and points within 5 miles of each of the named points, to points in Arkansas, Illinois, Indiana, Kentucky, Michigan, Missouri, Tennessee, and Wisconsin.

Note.—If a hearing is deemed necessary, the applicant requests it be held at Chicago, Ill., or Dallas, Tex.


Note.—If a hearing is deemed necessary, the applicant requests it be held at St. Louis, Mo.

No. MC 114211 (Sub-No. 278), filed July 31, 1976. Applicant: WARREN TRANSPORT, INC., 324 Manhard St., P.O. Box 420, Waterloo, Iowa 50704. Applicant's representative: Daniel Sullivan, 327 South LaSalle St., Chicago, Ill. 60604. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Lumber, lumber products, millworks, forest products and building materials, manufactured or distributed by lumber mills and lumber yards, from points in the United States (except Alaska and Hawaii), to points in the provinces of Manitoba, Saskatchewan and Alberta, Canada.

Note.—If a hearing is deemed necessary, the applicant requests it be held at either Fargo, N. Dak. or Minneapolis, Minn., with similar application of Arnold Bros. Transport, Ltd.

No. MC 114211 (Sub-No. 280), filed August 2, 1976. Applicant: WARREN TRANSPORT, INC., 324 Manhard St., P.O. Box 420, Waterloo, Iowa 50704. Applicant's representative: Daniel Sullivan, 327 South LaSalle St., Chicago, Ill. 60604. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Lumber, lumber products and pallets, from the plantsite and facilities of Smith Pallet Company, Inc., located at or near Hatfield, Ariz., to points in the United States (except Alaska and Hawaii).

No. MC 114233 (Sub-No. 2), filed July 19, 1976. Applicant: SOUTHERN TRUCKING CO., INC., P.O. Box 236, Clinton, Ind. 47642. Applicant's representative: Robert W. Loser, 1099 Chamber of Commerce Bldg., Indianapolis, Ind. 46204. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Crushed limestone, from points in Clark County, Ill., to points in Clay, Park, Vermillion and Wigo Counties, (a New York corporation).

Note.—If a hearing is deemed necessary, the applicant requests it be held at either Indianapolis, Ind., or Chicago, Ill.

No. MC 116495 (Sub-No. 31), filed July 26, 1976. Applicant: UNITED PARCEL SERVICE, INC., 390 North 2nd Street, St. Charles, Ill. 60174. Applicant's representative: S. Harrison Kahn, 733 Investment Bldg., 1511 K Street, NW., Washington, D.C. 20005. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: General commodities (except those of unusual value, classes A and B explosives, household goods as defined by the Commission, commodities in bulk and commodities requiring special equipment), (1) Between the premises of Montgomery Ward, Chicago, Ill., and Pembina and Dunseith, N. Dak., and Noyes, Minn., restricted to traffic moving by truck between points in the provinces of Manitoba, Saskatchewan and Alberta, Canada.

Note.—If a hearing is deemed necessary, the applicant requests it be held at either Fargo, N. Dak. or Minneapolis, Minn., with the application of Arnold Bros. Transport, Ltd.

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The premises of Sears, Roebuck and Co., Wisconsin, restricted to packages
originating at, or destined to the premises of Montgomery Ward's Catalog
Houses in Oakland, Calif.; Denver, Colo.; Chicago, Ill.; Baltimore, Md.; St. Paul,
Minn.; (except the plantsite of Morton Frozen Foods located at Russellville,
Ark., restricted in
(2) between points in Connecticut, Delaware, Maine, Maryland, Massachusetts,
New York, New Jersey, New Hampshire, Pennsylvania, Rhode Island,
Vermont, Virginia, West Virginia, and the District of Columbia.
(2) between points in Connecticut, Delaware, Maine, Maryland, Massachusetts,
New York, New Jersey, New Hampshire, Pennsylvania, Rhode Island,
Vermont, Virginia, West Virginia, and the District of Columbia, restricted to packages
originating at, or destined to the premises of Montgomery Ward's Catalog Houses
in Baltimore, Md.; Albany, N.Y.; Chicago, Ill.; Denver, Colo.; Ft. Worth, Tex.; Kansas
City, Mo.; Oakland, Calif.; Portland, Ore.; and Ft. Worth, Tex.; and further
restricted to packages having an immediately prior or, subsequent movement

(3) Between the premises of Sears, Roebuck and Co. Catalog Merchandise
Distribution Centers and their associated warehouses in Los Angeles, Calif.;
Jacksonville, Fl.; Atlanta, Ga.; Chicago, and Elk Grove Village, Ill.; Boston, Mass;
Memphis, Minn.; Minneapolis, Minn.; Greenboro, N.C.; Columbus, Ohio; Philadelphia, Pa.;
Memphis, Tenn.; Dallas, Tex.; and Seattle, Wash.; and further restricted to packages
having an immediately prior or subsequent movement by United Parcel Service, Inc., a New York corporation.

Restrictions: (a) No service shall be rendered in the transportation of any packages weighing 50 pounds or exceeding 48 inches in length and girth combined, and each package or article shall be considered as a separate and distinct shipment. (b) No service shall be provided in the transportation of packages or articles weighing in the aggregate more than 100 pounds from one consignor to one location on
any one day.

Note.—Applicant holds contract carrier authority in MC 13248 and subs thereunder, therefore dual operations may be involved. Common control may also be involved. If a hearing is deemed necessary, the applicant requests it held at New York, N.Y.

No. MC 116200 (Sub-No. 9), filed July 26, 1976. Applicant: UNITED PARCEL
SERVICE, INC., 643 West 43rd Street, New York, N.Y. 10020. Applicant's representative: S. Harrison Kahn, 733 Investment Bldg., 1511 K St., NW, Washington, D.C. 20005. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting:
General commodities (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk and commodities requiring special equipment), (1) between the premises of Montgomery Ward's Catalog Houses in Albany, N.Y., and Baltimore, Md., on the one hand, and on the other, points in Connecticut, Delaware, Maine, Maryland, Massachusetts, New York, New Jersey, New Hampshire, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and the District of Columbia. (2) between points in Connecticut, Delaware, Maine, Maryland, Massachusetts, New York, New Jersey, New Hampshire, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and the District of Columbia, restricted to packages having an immediately prior or subsequent movement by United Parcel Service, Inc., an Ohio Corporation.

(3) Between the premises of Sears, Roebuck and Co. Catalog Merchandise
Distribution Centers and their associated warehouses in Philadelphia, Pa.; Boston,

Note.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it held at New Orleans, La.

No. MC 117119 (Sub-No. 599), filed July 29, 1976. Applicant: WILLIE SHAW
FROZEN EXPRESS, INC., P.O. Box 158, Elm Springs, Ark. 72728. Applicant's representative: L. M. McLean (Same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Frozen foods, from the facilities of Morton Frozen Foods located at Crozet, Va., to the facilities of Morton Frozen Foods located at Russellville, Ark.; (A) frozen foods, from the facilities of Morton Frozen Foods located at Crozet, Va., to the facilities of Morton Frozen Foods located at Russellville, Ark.; (B) prepared flour (except in bulk), from Memphis, Tenn., to the facilities of Morton Frozen Foods located at Russellville, Ark.; and (C) prepared flour (except in bulk), from Memphis, Tenn., to the facilities of Morton Frozen Foods located at Russellville, Ark., restricted in
(2) to traffic originating at the named origin points and destined to the named destination points.

Note.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it held at Washington, D.C.

No. MC 117765 (Sub-No. 211), filed July 27, 1976. Applicant: HAHN TRUCK
LINE, INC., 5315 NW 5th St., P.O. Box 75218, Oklahoma City, Okla. 73107. Applicant's representative: R. E. Hagan (same address as applicant). Authority sought to operate as a common carrier, by motor vehicle, over irregular routes.
transporting: Scrap or waste paper, paper, and paper products, for recycling, from points in Iowa and Nebraska, to the plant of United States Gypsum Company, at North Platte, Nebr., and by motor vehicle, over irregular routes, transporting: General commodities (except foodstuffs), those of unusual value, explosives, household goods as defined by the Commission, in bulk, and those requiring special equipment, from Winona, Minn., to points in the United States (except Alaska and Hawaii); and (2) general commodities (except those of unusual value, classes A and B explosives, household goods as defined by the Commission, in bulk, and those requiring special equipment), from points in Connecticut, Delaware, Ohio, Pennsylvania, Tennessee, Maine, Massachusetts, Maryland, Michigan, Missouri, New Jersey, Nevada, New York, North Dakota, Ohio, Pennsylvania, South Carolina, and Wisconsin, and restricted in (1) above to shipments originating at the plant-sites of and warehouse facilities utilized by Watkins Products, Inc., located at Winona, Minn., and restricted in (3) above to shipments originating in the origin territory named above and destined to Watkins Products, Inc., located at Winona, Minn.

NOTE.—Applicant states that the purpose of this application is to convert presently held permits as a contract carrier authority to certificates as a common carrier and to operate in Minnesota and Wisconsin. Dual operations in Minnesota and Wisconsin do not affect the present application. Applicant presently holds extensive authority as a common carrier. If a hearing is deemed necessary, the applicant requests it be held at Minneapolis or St. Paul, Minn.

No. MC 118535 (Sub-No. 89), filed August 2, 1976. Applicant: TIONA TRUCK LINES, INC., 111 South Prospect, Butler, Pa. 16001. Applicant’s representative: William L. Williamson, 290 Foundation Life Bldg., 3535 NW 56th St., Oklahoma City, Okla. 73112. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Minerals, mineral mixtures, feed and fertilizer materials and compounds and ingredients therefor, from Galena, Kan., to points in Arkansas, Colorado, Illinois, Indiana, Iowa, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Mexico, North Dakota, Ohio, Oklahoma, South Dakota, Tennessee, Texas, and Wisconsin.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Kansas City, Mo.

No. MC 118561 (Sub-No. 19), filed July 20, 1976. Applicant: HERBERT B. FULLER, doing business as FULLER TRANSFER COMPANY, 212 East Street, Maryville, Tenn. 37801. Applicant’s representative: Robert E. Tate, P.O. Box 517, Evergreen, Ala. 36401. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Foodstuffs (except commodities in bulk), in mixed loads with meats, meat products, meat by-products, and articles distributed by meat packing houses, from the plant of Oscar Mayer & Co., Inc., at or near Goodlettsville, Tenn., to points in Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, South Dakota, Tennessee, Texas, and Virginia; and (2) materials, equipment, and supplies (except commodities in bulk), used in the manufacture, sale,
or distribution of foodstuffs, meats, meat products, meat by-products, and articles distributed by meat-packinghouses, from points in Kansas, Missouri, Oklahoma, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Virginia, and West Virginia, to the plantsite and storage facilities utilized by Oscar Mayer & Co., Inc., at or near Medford, Oregon or Medford, Tenn., restricted in part (1') above; to shipments originating at the named facilities and destined to points in States named.

Note.—If a hearing is deemed necessary, applicant requests it be held at Nashville, Tenn., or Washington, D.C.

No. MC 119832 (Sub-No. 70), filed July 29, 1976. Applicant: REED LINES, INC., 654 Rabston Avenue, Defiance, Ohio 43512. Applicant's representative: John F. McMahon, 100 East Broad Street, Columbus, Ohio 43215. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Food and food products, advertising matter, printed matter, and steel and paper cores, from Brookfield and New Berlin, Wis., to points in the United States (except Alaska and Hawaii); and (2) materials used or useful in the manufacture and distribution of the commodities named in (1) above, on return.

Note.—Applicant holds contract carrier authority in No. MC 140271 and subs thereunder, therefore, dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Milwaukee, Wis., Dallas, Tex., or Washington, D.C.

No. MC 119888 (Sub-No. 97), filed July 28, 1976. Applicant: GREAT WESTERN TRUCKING CO., INC., Highway 103 East, P.O. Box 1384, Lufkin, Tex. 75901. Applicant's representative: Clayte B. Elion, 1106 Continental Life Building, Fort Worth, Tex. 76102. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Paper, paper products, and wood pulp; and (2) materials and supplies used in the manufacture or conversion of those commodities specified in (1) above, between Houston and West Feliciana Parishes, La., on the one hand, and, on the other, points in the United States (except Alaska and Hawaii), restricted in (1) and (2) above against certain commodities in bulk, in tank vehicles.

Note.—Applicant holds contract carrier authority in MC 140271 and subs thereunder, therefore, dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either New Orleans or Baton Rouge, La.

No. MC 121496 (Sub-No. 2), filed July 23, 1976. Applicant: CANGO CORP., 110 Milam Building, Suite 2000, Houston, Tex. 77002. Applicant's representative: Eugene T. Lifpirt, 1601 Front St, New York, N.Y., 10036. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Petroleum products, in bulk, in tank vessels, including, but not limited to (1) petroleum products listed in Descriptions in Motor Carrier Certificates, 61 M.C.C. 206 (1952), and (2) acetylene; acetone; acetonitrile; aromatic distillate; alcohol; pyridine; aqua ammonia; butylene; butylene glycol; captain; chloroform; commercial cyclohexane; cyanohydrine; D.D.T. (technical); diallyl phthalate; dichloroacrylopropyl ethers; dicyclopentadiene; dichloroethylene glycol; dimethyl formamide; dimethylamine; diphenyl: dipropylene glycol; durene; ethane; ethyl chloride; ethyl chloride; ethyl chlorucc acid; ethyl cyanide; ethylene dibromide; ethylene oxide; ethylene dichloride; formalin; gasoline; glycine; glycerol dichlorohydrin; hexane; iso-butane; iso-pentane; isopropyl alcohol; ketone, methyl vinyl pyridine; liquid sulfur; methyl acetate; methyl alcohol; methyl chloride; methyl ethyl ketone; methyl ethyl-pyridine; methyl isobutyl carboline; methyl isobutyl ketone; methylene chloride; methyhlbenzene; paraformaldehyde; paraformic acid; paraformamide; paraffin wax; propylene; pyridine; pyrrole; pyrrole; styrene; styrene-butadlene latex; tetraethylene glycol; tetrachloroethylene; trichloroethylene; triethylene glycol; and tripropylene glycol; (a) Except points Texas (except Brooks, Cameron, Chambers, El Paso, Hidalgo, Jefferson, Jim Hogg, Kenedy, Kenedy, Newton, Orange, and Zapata Counties, Tex.) (b) From points in Brooks, Cameron, Chambers, El Paso, Hidalgo, Jefferson, Jim Hogg, Kenedy, Kleberg, Newton, Orange, Starr, Wallacy and Zapata Counties, Tex., to points in Texas.

Note.—Applicant states that the purpose of this application is to convert its Certificate of Registration to a Certificate of Public Convenience and Necessity. If a hearing is deemed necessary, the applicant requests it be held at Houston, Tex.

No. MC 121664 (Sub-No. 15), filed August 4, 1976. Applicant: HORNADY, CECIL M. HORNADY AND B. C. HORNADY, doing business as: HORNADY BROTHERS TRUCK LINE, P.O. Box 846, Monroeville, Ala. 36460. Applicant's representative: Gerald D. Hornaday, Jr., 630 Frank Nelson Building, Birmingham, Ala. 35203. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: General Commodities (except Explosives), from the facilities of National Cement Company, Inc., located at or near Ragland, Ala., and the facilities of Martin Marietta Cement Company, located at or near Roberia, Ala., to points in Florida, Georgia, Mississippi, Louisiana, Tennessee, North Carolina and South Carolina.

Note.—If a hearing is deemed necessary, the applicant requests it be held at either Birmingham or Mobile, Ala.

No. MC 123333 (Sub-No. 79), filed August 3, 1976. Applicant: BOYLE BROTHERS, INC., R.D 2, Box 329 C, Modford, N.J., 08051. Applicant's representative: Chester A. Zylpina, 384 Executive Building, 1030 Fifteenth Street, NW, Washington, D.C. 20005. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: General commodities (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk and commodities requiring special equipment), from the plantsite and storage facilities of Armstrong Cork Company located at E. Hempfield Township (Lancaster County), Pa., to points in Connecticut, Delaware, Maryland, Massachusetts, New Jersey, New York, Rhode Island, South Carolina, and Virginia, and District of Columbia, and refused and rejected shipments on return.
...the applicant requests that it be held at Washington, D.C.

No. MC 123675 (Sub-No. 3), filed June 24, 1976. Applicant: ELI L. SOLDIER AND JAMES W. WOODES, a partnership, doing business as SOLDIER BROS. AUTO BODY TRANSIT LINES, 614 Palme Avenue, Toledo, Ohio 43605. Applicant's representative: Arthur R. Cline, 420 Security Building, Toledo, Ohio 43604. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Railway passenger car seats, set up, wrapped; from Toledo, Ohio, to Philadelphia, Pa.


No. MC 124004 (Sub-No. 34), filed August 5, 1976. Applicant: RICHARD DAHN, INC., 620 West Mountain Road, Sparta, N.J. 07871. Applicant's representative: George A. Olsen, 69 Tonnele Ave., Jersey City, N.J. 07306. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Animal and poultry feed and animal poultry pet feed ingredients and cracklings, (1) between points in Delaware, Maryland, and Virginia, on the one hand, and, on the other, points in North Carolina and South Carolina; (2) from points in New York, New Jersey, and Pennsylvania, to points in South Carolina; (3) from points in Virginia, to points in Illinois, Indiana, Michigan, Minnesota, and Ohio and Wisconsin; and (4) from Silver City, N.C., Zanesville, Ohio, and Atlanta, Ga., to points in Connecticut, Delaware, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, and Virginia.

No. MC 125023 (Sub-No. 40), filed July 28, 1976. Applicant: SIGMA-4 EXPRESS, INC., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Paul F. Sullivan, 711 Washington Blvd., Washington, D.C. 20005. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Malt beverages, in containers, from Utica, N.Y., to points in Delaware, Maryland, North Carolina, Virginia and the District of Columbia; and (2) empty malt beverage containers in the reverse direction or on return.

No. MC 125738 (Sub-No. 60), filed August 2, 1976. Applicant: FLORIDA ROCK & TANK LINES, INC., P.O. Box 1559, 155 East 21st Street, Jacksonville, Fla. 32206. Applicant's representative: Martin Snook, Jr., 1241 Gulf Life Tower, Jacksonville, Fla. 32207. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Ground dolomite limestone and ground calcium limestone, in bulk, in dump trailers, from points in Jackson County, Fla., to points in Alabama and Georgia.


No. MC 128973 (Sub-No. 233), filed July 30, 1976. Applicant: MIDWESTERN DISTRIBUTION, INC., P.O. Box 189, 121 Humboldt St., Fort Scott, Kans. 66701. Applicant's representative: Elden E. Thorne and Ralston Streets, P.O. Box 3485, Wilson, N.C. 27893. Applicant's representative: Jack H. Blan- den, 205 West Touhy Avenue, Suite 200, Park Ridge, Ill. 60068. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Paper articles and paper products (except In bulk, in tank vehicles), from Richmond, Va., and Woburn, Mass., to points of entry on the International Boundary line between the United States and Canada, located in Maine, restricted to the transportation of shipments destined to points in the provinces of New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland, Canada.
Iton, Alberta, Canada, under contract Eastport, Idaho; and Sweetgrass, Mont., national Boundary line between the United States and Canada, located near Blaine, Lynden, and Sumas, Wash.; and between Oneonta, N.Y. on the one hand, and, on the other, William and Sidney, N.Y.; and between Onondaga, N.Y., on the one hand, and, on the other, Oswego, Cohoes, N.Y., and Baldwinsville, N.Y. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting:

- Dairy products, foods and foodstuffs and paper and plastic supplies used in restaurants and dairy stores, in containers in vehicles equipped with mechanical refrigeration, from Granite City, Ill., to points in Tennessee;
- Margarine, from Oceola, Ark., to Granite City, Ill.;
- Empty milk cartons, from Siloam, Mo., to Granite City, Ill.;
- Chocolate syrup, from Humboldt, Tenn., to Granite City, Ill.;
- Cheese, from Monett, Mo., to Granite City, Ill.;

(1) through (6) above are for the account of and under a continuing contract, or contracts, with P.F.D. Supply Corporation.

Note:—If a hearing is deemed necessary, the applicant requests it be held at either Columbus, Ohio, or New Orleans, La.

No. MC 134534 (Sub-No. 10), filed August 2, 1976. Applicant: L. LEESON, doing business as L. LEESON DISTRIBUTING, 1317-120, Hamilton, Ohio, 45011. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting:

- Pro-cast concrete products;
- Steel reinforcing bars, mesh and wire;
- Articles used in the manufacture, installation or construction of commodities described in (1) and (2) above, between the plants and warehouses of Con-Flax Corporation, a Division of U.S. Industries, Inc., located in Madison County, Miss., and points in Alabama, Mississippi, Arkansas, Louisiana, and Texas.

Note:—If a hearing is deemed necessary, the applicant requests it be held at either Columbus, Ohio, or New Orleans, La.
Walker Counties, Tex.,; Marble City, Mill Creek, and Sillsil, Ola.; Atoka, Beaver, Beulph, Lott, Okla.,; Cimarron, Craig, Custer, Dewey, Ellis, Greer, Harmon, Harper, Jackson, Kiowa, McClain, Major, Okla., Pucatuk, Robert, Miles, Okla.,; Washita, Wood and Woodward Counties, Okla.; and that between points in Oklahoma, restricted in (1), (2) and (3) above against the transportation of gravel from Pueblo County, Colo.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Oklahoma City, Okla.

No. MC 136247 (Sub-No. 12) (correction), filed July 9, 1976, published in the Federal Register issue of August 12, 1976, and republished as corrected this issue. Applicant: WRIGHT TRUCKING, INC., 401 17th Street SW., Jamestown, N. Dak. 58401. Applicant's representative: Jack R. Mills, 1600 Depobe Quaranty Plaza, P.O. Box 25628, Jackson, Miss. 33055. Applicant requests it be held at either Portland, Oreg., or Seattle, Wash.

NOTE.—The purpose of this republication is to amend applicant's requested authority. If a hearing is deemed necessary, the applicant requests it be held at either Portland, Oreg., or Seattle, Wash.

No. MC 136315 (Sub-No. 9), filed August 4, 1976. Applicant: OLEEN BURGESS TRUCKING, INC., Route No. 9, Box 22-A, Philadelphia, Miss. 38950. Applicant's representative: Fred W. Johnson., Jr., 1800 Depospe Quaranty Plaza, P.O. Box 25628, Jackson, Miss. 33055. Applicant requests it be held at Jackson, Miss.

NOTE.—The purpose of this amendment is to indicate the proper destination and republi- cation of this issue of Federal Register, No. 133106, to Valentine, N. Dak.

No. MC 136489 (Sub-No. 2), filed August 2, 1976. Applicant: RALPH L. NORTON, Rockford, Ill.; P.O. Box 27, Jericho, Vt. 05456. Applicant's representative: W. Norman Charles, 80 Bay Street, Glen Falls, N.Y. 12061. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Malt beverages, from Secaucus, N.J., and Fogelson, Pa., to Burlington, Vt.; (2) empty malt beverage containers, from Burlington, Vt., to Secaucus, N.J.; (3) soda, from Burlington, Vt., to Claremont, N.H., and Malone and Ogdensburg, N.Y.; (4) empty glass bottles, from New York, N.Y., and Gliensaw, Pa., to Burlington, Vt., and (5) wine, from Bremerton, N.J., and Long Island City, N.Y., to Burlington, Vt.; (1) through (5) above are under a continuing contract, or contracts, with Vermont Fruit & Grocery Company, Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Burlington or Montpelier, Vt.

No. MC 138144 (Sub-No. 11), filed August 5, 1976. Applicant: FRED OLSON CO., INC., 6023 W. 36th Street, Milwaukee, Wis. 53218. Applicant's representative: Daniel C. Sullivan, 337 South La Salle Street, Chicago, Ill. 60604. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Iron and steel articles; (2) materials and supplies used in the manufacture and distribution of electric motors and generators, from Carrollville, Wis., to Waukesa, Wis.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Milwaukee, Wis., or Chicago, Ill.

No. MC 138255 (Sub-No. 5), filed August 2, 1976. Applicant: INTERIOR TRANSPORT, INC., P.O. Box 3347, 2104 Waterworks Way, Spokane, Wash. 99202. Applicant's representative: George H. Hart, 1100 IBM Bldg., Seattle, Wash. 98102. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: (1) Metal building materials, from Minneapolis, Minn., to points in Arizona, California, Colorado, Idaho, Illinois, Iowa, Kansas, Minnesota, Montana, Nebraska, Nevada, New Mexico, North Dakota, Oklahoma, Oregon, South Dakota, Texas, Utah, Washington, Wisconsin, and Wyoming, under a continuing contract, or contracts, with Clifford-Hill Company, Inc.; and (2) steel coil, from points in California, Oregon, Utah, and Washington, to Minneapolis, Minn., under a continuing contract, or contracts, with Clifford-Hill Company, Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Seattle or Spokane, Wash.

No. MC 138741 (Sub-No. 24), filed August 4, 1976. Applicant: E. K. MOTOR SERVICE INC., 910 Broadflfcld Bldg., 101 West 11th St., Kansas City, Mo. 64105. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Building materials (except commodities in bulk), from the plantsite, shipping and warehouse facilities of GAP Corpora- tion, in Posey and Vanderburgh Count- ies, Ind., to points in Arkansas, Iowa, Kansas, Nebraska, Oklahoma, and Wis- consin.

NOTE.—Common control may be involved. If a hearing is deemed necessary, applicant requests it be held at Chicago, Ill., or Washing- ton, D.C.

No. MC 138495 (Sub-No. 156), filed August 3, 1976. Applicant: NATIONAL CARRIERS, INC., 1501 East 5th Street, P.O. Box 1389, Liberal, Kansas, 67901. Applicant's representative: Herbert Alan Dubin, 1819 H St. NW, Suite 1030, Wash- ington, D.C. 20006. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Personal care products, from the facilities of the Warner-Lambert Company, located at or near Milford and Orange, Conn., to the facilities of Warner- Lambert Company, located at or near Little, Pa.; Elk Grove Village, Ill.; Grand Prairie, Tex.; Anaheim, Calif.; and Mil- waukee, Oreg., restricted to shipments originating at and destined to the fa- cilities of the Warner-Lambert Company.

NOTE.—Applicant holds contract carrier authority in MC 133106 and sub theretofore, therefore, dual operations may be involved. If a hearing is deemed necessary, applicant requests it be held at Washington, D.C.

No. MC 134592 (Sub-No. 9), filed August 7, 1976. Applicant: HERB MOORE
AND HAZEL MOORE, doing business as H & H TRUCKING CO., 10380 North Vancouver Way, Portland, Ore. 97217. Applicant's representative: Robert G. Simpson, 718 Maryland Avenue, Portland, Ore. 97204. Authority sought to operate as a "common carrier," by motor vehicle, over irregular routes, transporting: Wine, champagne, beer, and curbstone, paving and construction materials, flower boxes, pots, and containers, from points in California, on the one hand, and, on the other, points in Idaho, Oregon, and Washington.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Portland, Ore., San Francisco, Calif., or Seattle, Wash.

No. MC 129888 (Sub-No. 8), filed July 22, 1976. Applicant: AMSTAN TRUCKING INC., 1255 Corvin Avenue, Hamilton, Ohio 45011. Applicant's representative: Chandler L. Van Orman, 704 Southern Building, Washington, D.C. 20005. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: General commodities (except commodities in bulk, those of unusual value, Classes A and B explosives, household goods as defined by, and those which require the use of special equipment), from the warehouse and distribution facilities of American Standard, located at Hamilton, Ohio, to points in and west of Colorado, Montana, New Mexico, and Wyoming, under a continuing contract, or contracts, with American Standard, Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Cincinnati, Ohio, or Washington, D.C.


NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Philadelphia, Pa., or Washington, D.C.


NOTE.—Applicant holds contract carrier authority in No. MC 140781, therefore, dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at New York, N.Y.

No. MC 141114 (Sub-No. 1), filed July 21, 1976. Applicant: RETAILERS DELIVERY FACILITY CO., INC., 801 Washington Street, Wilmington, Del. 19899. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Garden supplies, lawn ornaments, lawn tools, as- cendents, and containers, from the warehouse, and the United States on and west of a line beginning at the mouth of the Hudson River where it joins the Atlantic Ocean, thence northerly along the east bank of the Hudson River, over U.S. Highway 9, to the international boundary line between the United States and Canada, to points in the United States in and east of Arkansas, Iowa, Minnesota, Missouri, and Texas, under a continuing contract, or contracts, with Lawn & Garden Shops Co., Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 141141 (Sub-No. 4) (Amendment), filed August 9, 1976, published in the Federal Register Issue of August 9, 1976, and republished as amended this issue. Applicant: NAVAJO LINE, INC., Route No. 1, Moncure, N.C. 27559. Applicant's representative: Moncure, N.C. 27559. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Clay products (except commodities in bulk), on special I-beam flatbed trailers with hydraulic unloaders, (1) from points in Chatham and Wake Counties, N.C., to points in Ohio and West Virginia; (2) from Nitro, W.Va., Coal Grove, Ohio and Minerva, Ohio, to points in North Carolina, South Carolina, Virginia, and Maryland; (3) from points in York County, S.C., to points in North Carolina, South Carolina, Virginia, and West Virginia, under a continuing contract, or contracts, with Cherokee Brick Company of North Carolina.

NOTE.—The purpose of this republication is (A) to indicate the correct name of the Applicant as "Navajo Line, Inc." in lieu of "Navajo Lines, Inc." as previously published; (B) to indicate in part (2) of the territorial description the origin point of Coal Grove, Ohio in lieu of Ironclad, Ohio. If a hearing is deemed necessary, the applicant requests it be held at either Raleigh, N.C. or Washington, D.C.

No. MC 141759 (Sub-No. 4), filed August 9, 1976. Applicant: OHIO PACIFIC EXPRESS, INC., 6914 Conservation Drive, Springfield, Va. 22153. Applicant's representative: Thomas F. Kilroy, P.O. Box 624, Springfield, Va. 22155. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Plastic materials, plastic articles and chemical compounds (except in bulk), in tank attack vehicles, between Ohio, Ill. and Morgan, Parkersburg, and Washington, W.Va., on the one hand, and, on the other, points in Alabama, Arkansas, California, Connecticut, Delaware, Georgia, Indiana, Iowa, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Mississippi, Missouri, New Jersey, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, and West Virginia, under a continuing contract, or contracts, with Borg-Warner Chemicals.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Columbus, Ohio.

No. MC 141918 (Sub-No. 5), filed August 2, 1976. Applicant: AURELIA TRUCKING CO., Inc., Route No. 1, Pine Grove Avenue, Port Huron, Mich. 48060. Applicant's representative: Robert D. Schuler, 100 West Long Lake Road, Suite 102, Bloomfield Hills, Mich. 48013. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Foodstuffs (except in bulk), from Duluth, Minn, to points in Illinois, Indiana, and Michigan, restricted against transportation between points in California, Illinois, Michigan or Washington, D.C.

NOTE.—Applicant holds common carrier authority in No. 117836, and seeks the above, therefore dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Detroit, Mich., Chicago, Illinois or Washington, D.C.

No. MC 142071 (Sub-No. 1), filed July 28, 1976. Applicant: AMERICAN TERMINALS, INC., 1187 N. Kraemer Blvd., Anaheim, Calif. 92806. Applicant's representative: Stanisa J. Ferkich, 1200 World Trade Center 233 S. Flower St., Los Angeles, Calif. 90071. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Swimming pool and floor ing glazed and quarry tile products and related bonding materials, (1) between the plantsite of Quality Marble and Tile Company, located in Atlanta, Ga., Baltimore, Md., Dallas, Tex., Denver, Colo., Kansas, Phoenix, Ariz., and Anaheim, N. Hollywood, Sacramento, San Diego, and San Leandro, Calif.; (2) from the plantsite of U.S. Company located in Houston, Miss., and Canton, Ohio, to the plantsite of Quality Marble and Tile Company as listed in paragraph (1) above; (3) from the plantsite of Chicago Motors located in Hamilton, Ohio, to the plantsite of Quality Marble and Tile Company as listed in paragraph (1) above; (4) from Miami, Fla., Mobile, Ala., and Long Beach, Los Angeles, Oakland, San Francisco and San Pedro, Calif., to the plantsite of Quality Marble and Tile Company as listed in paragraph (1) above, restricted against transportation between points in California.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Washington, D.C. or San Francisco, Calif.

NOTICES

Seattle, Wash. 98101. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Furniture, machinery, from points in California, located at or near Joyce, La., to points or in paper, polyurethane and/or sisal, to points in Oklahoma, Tennessee, and Texas.

No. MC 142134, filed July 21, 1976. Applicant: EVANS TRUCKING, INC., 52 Harrison Ave, Branford, Conn. 06405. Applicant's representative: William J. Avruch, 86 Cherry St, P.O. Box 187, Milford, Conn. 06460. Authority sought to operate as a contract carrier, by motor vehicle, over irregular routes, transporting: Powdered shale (aggregate), between Cohoes and Saugerties, N.Y., on the one hand, and, on the other, Westbrook, Conn., under a continuing contract, or contracts, with Westbrook Concrete Block Co., Inc.


No. MC 142207 (Sub-No. 1), filed July 29, 1976. Applicant: GULF COAST TRUCK SERVICES, INC., P.O. Box 29424, New Orleans, La. 70189. Applicant's representative: Bruce E. Mitchell, 3379 Peachtree Rd., N.E., Suite 3375, Atlanta, Ga. 30326. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Lumber, lumber and wood products, from the facilities of Crown Zellerbach, located at or near Joyce, La., to points in Alabama, Arkansas, Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Ohio, Oklahoma, Tennessee, and Texas.

Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Furniture, machinery, from California, to points in Texas, restricted to traffic having a prior movement by rail.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Seattle, Wash.

No. MC 59717 (Sub-No. 8), filed August 4, 1976. Applicant: JACKSONVILLE BUS Lines Co., a Corporation, 2106 East 4th Street, Jacksonville, Fla. 32203. Applicant's representative: Melvin Routman, 306 Relish Building, Springfield, Ill. 62702. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Passengers, and their baggage in the same vehicle with passengers, in charter and special operations, in all expense sightseeing and pleasure tours, between points in Hancock, McDonough, Fulton, Peoria, Tazewell, Mason, Menard, Sangamon, Cass, Brown, Schuyler, Adams, Morgan, Calhoun, Pike, Scott, Macoupin, Greene, Jersey, Montgomery, Madison, St. Clair, Logan, McLean and DeWitt Counties, Ill., Marion, Lewis and St. Louis Counties, Mo., including the St. Louis-East St. Louis, Mo.-Kans. Commercial Zone and Lee County, Iowa, on the one hand, and, on the other, points in the United States, including Alaska but excluding Hawaii.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Springfield, Ill. The application is filed with applicant's representative, or applicant if no representative is named.

No. MC 84697 (Sub-No. 1), filed June 25, 1976. Applicant: LEIPHAFT BUS COMPANY, INC., R.R. No. 12, Branch, York, Pa. 17406. Applicant's representative: Penny Bonadonna, 141 E. Market Street, P.O. Box 709, York, Pa. 17405. Authority sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: Passengers and their baggage, in groups, in charter operations, between York, Pa., and points within 15 miles thereof, in New York, North Carolina, Ohio, Virginia and West Virginia.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either York, Hanover, or Gettysburg, Pa.

No. MC 130198 (Sub-No. 1), filed August 2, 1976. Applicant: ROBERT GAVIN & ASSOCIATES, INC., 2550 South Kinlock Avenue, Milwaukee, Wis. 53207. Applicant's representative: F. Thomas Olson, 211 West Wisconsin Avenue, Milwaukee, Wis. 53203. Authority sought to engage in operation, in either foreign commerce, as a broker at Milwaukee, Wis., to sell or offer to sell the transportation by motor, rail, water or air carriers, of individual passengers and groups of passengers, and their baggage, in special and charter operations, in round-trip, all-expense tours, beginning and ending at points in Adams, Brown, Calumet, Columbia, Dane, Dodge, Fond du Lac, Green Lake, Jefferson, Langlade, Lincoln, Manitowoc, Marathon, Marquette, Oneida, Outagamie, Ozaukee, Portage, Walworth, Waupaca, Washington, Winnebago and Wood Counties, Wis., and extending to points in the United States, including Alaska and Hawaii.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Milwaukee, Madison or Green Bay, Wis.

FINANCE APPLICATIONS

The following applications seek approval to consolidate, purchase, merge, lease operating rights and properties, or acquire control through ownership of stock, of rail carriers or motor carriers pursuant to Sections 211(a) and 211(a)(b) of the Interstate Commerce Act.

An original and two copies of protests to the granting of the requested authority must be filed with the Commission on or before October 12, 1976. Such protest shall comply with Special Rules 240(o) and 240(d) of the Commission's General Rules of Practice (49 CFR § 1000.340) and shall include a concise statement of protestant's interest in the proceeding. A copy of the protest shall be served concurrently upon applicant's representative, or applicant if no representative is named.

No. MC-7-12913, Authority sought for purchase by RYDER TRUCK LINES, INC., 2550 Kings Road, Jacksonville, FL, 32203, of a portion of the operating rights of ASSOCIATED TRANSPORT, INC., THOMAS C. BANKRUPTCY, c/o Arthur S. Olick, 39th Floor, 630 Fifth Avenue, New York, N.Y., 10020, and for acquisition by IU TRANSPORT SERVICES, INC., 1105 N. Market St., Wilmington, Del., 19801, The Wilmington Tower, which is in turn controlled by IU INTERNATIONAL CORPORATION, The Wilmington Tower, 1105 N. Market St., Wilmington, Del., 19801, of control of such rights through the purchase, Applicants' attorneys: Henry Chadwick, 1500 Walnut Street, Philadelphia, Pa. 19102, Roland Rice, Suite 550, 2910 Perpichalide, Washington, D.C. 20004, and Fritz R. Kahn, 1669 L Street, NW, Washington, D.C. 20036. Operating rights sought to be transferred: General commodities with exceptions as a common carrier over irregular routes between points in Suffolk and Middlesex Counties, Mass., on the one hand, and, on the other, points in New Hampshire; and, on the one hand, and, on the other, points in New Hampshire, moving through Boston, Mass., and
points within 10 miles of Boston, in Suffolk and Middlesex Counties; between points in that part of Maine, on and south of a line beginning at the New Hampshire-Maine State line, and extending along Maine Highway 16 to junction unnumbered highway (formerly portion Maine Highway 16) near Howland, thence along Maine Highway 6 to the United States-Canada Boundary line at New Brunswick, on the one hand, and, on the other, points in that part of Massachusetts beginning at a point on and east of a line and extending in a general northerly direction along Massachusetts Highway 32 to junction Massachusetts Highway 2, thence along Massachusetts Highway 2 to junction Massachusetts Highway 78, and thence along Massachusetts Highway 78 to the Massachusetts-New Hampshire State line, except points in Hampden County, and those on Cape Cod east and south of Cape Cod Canal; between points in Massachusetts, on the one hand, and, on the other, points in New Hampshire, moving through Suffolk and Middlesex Counties, Mass., any duplication of authority granted hereinafter or to the extent that such authority duplicates any heretofore granted to or or to the extent that such authority is a common carrier, in interstate commerce, within the State of Connecticut. Vendee is authorized to operate as a common carrier in -Connecticut, New York, and New Jersey. Application has been filed for temporary authority under section 210a(b).

Note.—No. MC-73616 (Sub-No. 3) is a directly related matter.

No. MC-F-12947. Authority sought for control and merger of McLEAN TRUCKING CO., 617 Corlies Avenue, Neptune, N.J., 07762, and John L. Alfano and Edward M. Alfano, 550 Main Avenue, Har-

TOM'S HARTFORD EXPRESS, INC., 1 Cooper Lane, Stafford Springs, CT, 66016, and for control and merger of J. KORIENTHANUS, 510 Bowne Rd., Way-

side, N.J., 07712, and ROBERT A. KORIENTHANUS, 18 Pitney Ave., Spring Lake, N.J., 07762, of consolidated authority under section 210a(b). Operating rights sought to be transferred: Under a certificate of registration in Docket No. MC-57346 (Sub No. 1) covering the transportation of general commodities, as a common carrier, in interstate commerce, within the United States (except Alaska and Hawaii). Application has been filed for temporary authority under section 210a(b).

Note.—No. MC-T-73616 (Sub-No. 3) is a directly related matter.

No. MC-F-12923. Authority sought for purchase by JACK B. KELLEY, INC., Route 1, Box 406, Amarillo, TX 79106, of a portion of the operating rights of FAIRWAY TRANSIT, INC., N. 10 W. 24730 Highway TJ, Pewaukee, WI 53072, and for acquisition by JACK B. KELLEY, of Amarillo, Texas-Canada Boundary line, control of and power to purchase. Applicants' attorney: Austin L. Hatchell, 1102 Perry Brooks Bldg., Austin, TX 78701. Operating rights sought to be transferred: Liquid Common Carrier in interstate commerce, including District of Columbia, but excluding Alaska and Hawaii. Application has been filed for temporary authority under section 210a(b).

Note.—No. MC-123589 (Sub-No. 69) is a directly related matter.

No. MC-F-12946. Authority sought for purchase by JAMES STAYS EXPRESS, CO., 439 Old Corlies Avenue, Neptune, N.J., 07753, of the operating rights of BEN-
NOTICES

Act for approval of an agreement between common carriers for the pooling of traffic. Applicants: CONSOLIDATED FREIGHTWAYS CORPORATION OF DELAWARE, P.O. Box 174, Wilmington, DE 19899, and FREDERICK J. PERRY, 1645 Park, CA, 94025 (MC-42485). (A) BESTWAY MOTOR FREIGHT, INC, 1765 6th Avenue, South Seattle, WA, 98134 (MC 9236), SUMAS & EVESON AUTO FREIGHT INC, 210a 25th Avenue S, Seattle, WA 98144 (MC 96230), (B) WALLACE-COLVILLE MOTOR FREIGHT, INC, N. 400 Sycamore, Spokane, WA, 99202 (MC 19243), (C) OAK HARBOR FREIGHT LINES, 6400 South 143rd, Seattle, WA 98178, (MC 139763), (D) EVERGREEN FREIGHT LINES, INC, 820 E. Union Avenue, Spokane, WA, 99205 (MC 135604), (E) EASLETT COMPANY, 224 Union Street, Oakland, CA, 94607, and (F) VICTORVILLE-BARSTOW TRUCK LINE, 4366 E 26th Street, Los Angeles, CA, 90033 (MC 97666), seeks to enter into an agreement for the pooling of traffic consisting of (A) general commodities, frozen and processed fruits, vegetables, and horticultural products, and horticultural products, frozen and processed fruits, vegetables, and horticultural products, transported over and between points in the States of Montana, Wyoming, Colorado and New Mexico, in parts, as follows: Othello, Warden, Moses Lake, Soap Lake, Ephrala, Quincy, Grant Orchards, Grant County Airport, Wheeler, Westlake, and Bruce, (B) between Acme, Deming Everson, Nocksack, and Sumas, Washington, (C) between (Part I points located on U.S. Highway 16 (Interstate Highway 90) between Post Falls, Idaho and the Idaho-Montana State line, including Post Falls. (Part II) points located on U.S. Highway 95 between Dalton Gardens, Idaho and Bonners Ferry, Idaho including Dalton Gardens and Bonners Ferry. (Part III) Moylespings Idaho, Troy, Montana, Libby, Montana, points of interchange, Spokane, Washington—(1) All traffic destined to points I above, (2) All traffic destined to points in Part II above located on U.S. Highway 95 between Dalton Gardens, Idaho and Sandpoint, Idaho, excluding Sandpoint. (3) All traffic destined to points in Parts I, II and III originating west of the western boundaries of the States of Montana, Wyoming, Colorado and New Mexico, Kallis, Montana—(1) All traffic destined to points in Part III above which originates east of the western boundaries of the States of Montana, Wyoming, Colorado and New Mexico. Representative points; Post Falls, ID, Kingston, ID, and Coeur d'Alene, ID. (2) Eagle, ID, Smelterville, ID, Osburn, ID, Wallace, ID, Mullan, ID, Sandpoint, ID, Bonners Ferry, ID, Moylespings, ID, Troy, MT, Libby, MT; (D) Allen, Big Lake, Birch Bay, Blaine, Bow, Chuckanut, Conway, Custer, Edison, Lynden, Montebonne, and Samish, WA.; (E) Reedman, Deep Creek, Davenport, Harlowton, Hinsdale, Idaho Creek, Independence,Marian, Stratford, Coles City, Hartline, Almira, Wilbur, Creston, Lincoln (City), Electric City, Grand Coulee, Coles City, Kettleworth, and Sprague, WA; (F) all intermediate points in the United States between the termini of Interstate 5 and California Highway 104 to and including Toluca, California, and (G) Highway 1 to and including Toluca, California.  (Part III—Traffic to following points to be interchanged at Eugene, Oregon: Blue River, OR, Cougar Dam, McKenzie Bridge, and Riddle, OR, and for control and merger, (Part IV—Traffic to following points to be interchanged at Los Angeles, California: West Yuma, AZ, Victorville, Barstow, Rialto, Los Angeles, CA, Air Force Base, Marine Corps Supply Center, Newberry Springs, Ora Grande, Hodge, Lenwood, and Hesperia, CA. Applicants' attorneys: Clyde L. Libby, Libby, MT; Wallace, NC, serving the Intermediate points of That part of California south of a line drawn east and west through Chico, Calif., with no transportation for compensation on return except as otherwise authorized, between King and Pierce Counties, Washington, and Oregon, Multnomah, and Washington Counties, Oreg., to points in that part of California south of a line drawn east and west through Chico, Calif.; agricultural and horticultural products, from points regularly routes between Shelby, N.C., and points in North Carolina within 25 miles thereof; between Shelby, N.C., and points in North Carolina within 25 miles of North Carolina east of U.S. Highway 221; and on and west of U.S. Highway 220.  Vendor is authorized to operate as a common carrier over regular routes between Seattle, Wash., and Los Angeles, Calif., serving the Intermediate points of Tacoma, Wash., and Chehalis, Wash., Portland and Medford, Oreg., and Sacramento, San Francisco, Stockton, Fresno, and Bakersfield, Calif, with restrictions; commodities requiring refrigeration, over alternate routes for operating convenience only, between Tacoma, Wash., and Tenino, Wash., serving no Intermediate points or the term except as otherwise authorized, between Gothenburg, Oreg., and Weeds, Calif., serving no Intermediate points or the term except as otherwise authorized, between San Francisco, Calif., and Los Angeles, Calif., serving the Intermediate points or the term except as otherwise authorized, between Gilroy, Calif., and Jackson California Highway 155 and U.S. Highway 99 serving no intermediate points or the term except as otherwise authorized, between fish and seafoods, as a common carrier over irregular routes from Westport and Ilwaco, Wash., to points in that part of California south of a line drawn east and west through Chico, Calif., with no transportation for compensation on return except as otherwise authorized, fish, fresh, frozen, smoked, and salted, fish oil; poultry, poultry, agricultural and horticultural products, frozen and processed fruits, berries, and vegetables, from points in King and Pierce Counties, Washington, and Multnomah, and Washington Counties, Oreg., to points in that part of California south of a line drawn east and west through Chico, Calif.; agricultural and horticultural products, from points
in that part of California south of a line drawn east and west through Chico, Calif., to points in that part of Oregon and Washington west of the Cascade Mountains; fish, from Eureka, California, to Portland, Oregon, and at the same time with frozen foods in that part of California south of a line drawn east and west through Chico, Calif., to Seattle, Wash.

Lumber, from points in Curry County, Oreg., and points in Oregon within five miles of Curry County, and from Bandon, Oreg., to points in California; frozen fruits, frozen vegetables, and frozen berries, between points in California, Oregon, and Washington, from points in Oregon and Washington, to Phoenix, Tucson, and Safford, Ariz., and Las Vegas and Reno, Nev., from Nampa and Lewiston, Idaho, to points in Oregon and California; bananas, fresh fruits, and fresh vegetables, in mixed loads, from Los Angeles, Calif., to Portland, Oreg.; fish, in mixed loads with frozen fruits, frozen vegetables, and frozen berries, from Hillsboro, Oreg., to Phoenix and Tucson, Ariz.; frozen foods (except frozen fruits, frozen vegetables, and frozen berries) from Yakima, Umatilla, Multnomah, Marion, and Washington Counties, Oreg., on the one hand, and, on the other, Phoenix and Tucson, Ariz., and Portland, Wash., and Phoenix, Ariz.; bananas and fresh fruits, fresh vegetables, and fresh berries, when moving in the same vehicle with bananas, from points in California, to Pendleton, Oreg., Lewiston, Idaho, and points in Washington east of the Cascade Mountains; frozen foods and potato products, not frozen, from points in Oregon and Washington to points in California and Phoenix, Safford, and Tucson, Ariz.; frozen foods, except frozen fruits, vegetables and berries, from Ventura, Corona, Modesto, and Ontario, Calif., to Seattle, Wash., and Portland, Oreg.; canned goods, between Sherwood, Oreg., on the one hand, and, on the other, Vancouver, Wash., and points in Multnomah, Polk, and Benton Counties, Oreg. and maternal counties, Ore., and points in Washington east of the Cascade Mountains; frozen foods and potato products, not frozen, from points in California, to Bend and Klamath Falls, Oreg., canned fruits, berries, and vegetables, from points in Folk, Lane, Benton, and Umatilla Counties, Oreg., and Vancouver and Columbia Counties, Wash., to points in that part of California south of a line drawn east and west through Chico, Calif.; frozen foods, from points in California, to Spokane, Wash.

Frozen prepared vegetables, from points in California, to Portland, Oregon, and points in Yamhill, Multnomah, Marion, and Washington Counties, Oreg., from points in Oregon to points in California, to Portland, Oregon, and points in Yamhill, Umatilla, Multnomah, Marion, and Washington Counties, Oreg., to Seattle, Wash., and Phoenix and Tucson, Ariz., from points in Washington to points in California, to Portland, Oregon, to Wallowa, Umatilla, Multnomah, Washington, and Yamhill Counties, Oreg., from Walla Walla, Wash., to Phoenix, Ariz., from Nampa, Idaho, to Ellensburg, Wash., and Portland, Oreg., and San Francisco, Calif., from points in Oregon and Washington, to Phoenix, Safford, and Tucson, Ariz., and points in California; foodstuffs (except in bulk) from Kansas City, Wash., to points in Nevada; foodstuffs (except in bulk, in tank vehicles), from the plantsite of Welch Foods Company at Gresham, Portland, Salem, Stayton, Silverton, Springfield, Bandon, and Canton, Oreg., to points in Nevada, meat, meat products, and meat by-products, as described in section 200 of Appendix I to the report in Descriptions in Motor Carrier Certificates, 61 M.C.C. 209 and 766, from Wallula and Walla Walla, Oreg., to points in California, from Seattle, Wash., to points in Oregon and Arizona, from Ellensburg, Wash., to points in California and Oregon, from Louisville, Oreg., to points in California and Washington, canned goods, from Walla Walla, Wash., to points in California from Vancouver, Wash., and points in Benton, Lane, Polk, Marion, Multnomah, Umatilla, and Washington Counties, Oreg., to points in that part of California north of a line drawn east and west through Chico, Calif.; bananas, from Seattle, Wash., to points in Oregon, Idaho, Washington, and Montana, from points in California, to La Grande, Oreg.; frozen foods, from the plantsite and storage facilities utilized by Lamb-Weston, Inc., division of Amfac, Inc., at points in Oregon, Oregon, Franklin, Grant, and Walla Walla Counties, Wash., to points in Oregon and Washington, and those in Washington; frozen meats, wine, (except in bulk), and processed foods, from Prosser, Wash., to points in Oregon, California, Arizona and Nevada; pet food, in containers, from Long Beach, Terminal Island, and Vernon, Calif., to points in Oregon and Washington.

Canned seafoods and pet foods, from Bellingham, Wash., and Astoria, Oreg., to points in Arizona and California; meat, meat products, and meat by-products, and articles distributed by meat packhouses, as described in Sections A and C of Appendix I to the report in Descriptions in Motor Carrier Certificates, 61 M.C.C. 209 and 766 (except hides and commodities in bulk), from Spokane, Wash., to points in Oregon and California; containers, in mixed loads with frozen foods, and commodities the transportation of which is partially exempt pursuant to the provisions of section 200(b) of the Interstate Commerce Act, when moving in the same vehicle with bananas, from points in California, to Pendleton, Oreg., Lewiston, Idaho, and points in Washington east of the Cascade Mountains; frozen foods and potato products, not frozen, from points in California, to Bend and Klamath Falls, Oreg., canned fruits, berries, and vegetables, from points in Folk, Lane, Benton, and Umatilla Counties, Oreg., and Vancouver and Columbia Counties, Wash., to points in that part of California south of a line drawn east and west through Chico, Calif.; frozen foods, from points in California, to Spokane, Wash.

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976

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La Conner, Wash., to Salem, Oregon, and (MC 114286 Sub-80) pet food in containers from San Diego, Calif., to points in Oregon and Washington. NAVJO FREIGHT LINES, INC., is authorized to operate as a commodity carrier over regular routes between and including New York, N.Y., and those points in New York, in the New York, Tennessee, Kentucky, Ohio, and Michigan State line; application has not been filed for temporary authority under section 210(c).

No. MC-112373 (Sub-No. 253), filed August 10, 1976. Applicant: CREST INC., P.O. Box 68, Cedar Rapids, Iowa. Applicant's representative: Robert E. Konchar, Suite 315 Commerce Exchange Building, Cedar Rapids, Iowa. Authority is sought to operate as a common carrier, by motor vehicle, over irregular routes, transporting: (1) Meat, meat products, and meat articles distributed by meat packinghouses, as described in Sections A and C of Appendix I to the report in Descriptions in Motor Carrier Certificates, 61 M.C.C. 209 and 766, except commodities in bulk, classes A and B explosives, household goods as defined by the Commission, and those requiring special equipment; between that part of Michigan on, west and north of a line beginning at the Indiana-Michigan State line extending along Indiana Highway 39 to the junction of Indiana Highway 10, thence along Indian Highway 10 to the Illinois-Indiana State line.

General commodities, (except commodities in bulk, classes A and B explosives, household goods as defined by the Commission, and those requiring special equipment), between that part of Michigan on, west and south of a line beginning at the Indiana-Michigan State line extending along Michigan Highway 47 to Saginaw, thence along Michigan Highway 48 to St. Louis, thence along U.S. Highway 27 to Marshall, thence along Michigan Highway 94 to the junction of Michigan Highway 66, thence along Michigan Highway 66 to the Indiana-Michigan State line, located at Midland, Mich., and Toledo, Ohio, on the one hand, and, on the other, that part of Indiana on, west and north of a line beginning at the Indiana-Michigan State line extending along Indiana Highway 15 to the junction of Indiana Highway 25, to the junction of Indiana Highway 28, thence along Indiana Highway 28 to the junction of U.S. Highway 41, thence along U.S. Highway 41 to the Indiana-Kentucky State line; (9) General commodities (except commodities in bulk, classes A and B explosives, household goods as defined by the Commission, and those requiring special equipment), between that part of Pennsylvania on and west of U.S. Highway 119 and on and south of U.S. Highway 422, and Delaware, Pennsylvania, Ohio, on the one hand, and, on the other, that part of Indiana on, west and south of a line beginning at the Indiana-Michigan State line extending along Indiana Highway 39 to the junction of Indiana Highway 10, thence along Indiana Highway 10 to the Illinois-Indiana State line.

October 12, 1976. Such protests shall comply with Special Rule 247(d) of the Commission's General Rules of Practice (49 CFR §1100.247) and include a concise statement of protestant's interest in the proceeding and copies of its conflicting statements in the record. 'A copy of the protest shall be served concurrently upon applicant's representative, or if no representative is named.

Each applicant shall file an answer, in writing, to any protest filed, within 10 days after service of the protest.

Each protest shall be served on the Commission, a copy of which shall be sent to each applicant.

Each protest shall state the ground(s) of protest.

Each protest shall state the relief sought.

Each protest shall state the name and address of the protestant.

Each protest shall state the name and address of the protestant's representative, if any.

Each protest shall state the time at which and the place where the protestant will be present, if any.

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The following operating rights applications are filed in connection with pending finance applications under Section 5(2) of the Interstate Commerce Act, or seeking exemption and/or gateway elimination, in connection with pending transfer applications under Section 212(b) of the Interstate Commerce Act.

Operating Rights Applications Directly Related to Finance Proceedings

The following operating rights applications are filed in connection with pending finance applications under Section 5(2) of the Interstate Commerce Act, or seeking exemption and/or gateway elimination. In connection with pending transfer applications under Section 212(b) of the Interstate Commerce Act.

An original and two copies of protests to the granting of the authorities must be filed with the Commission on or before

October 12, 1976. Such protests shall comply with Special Rule 247(d) of the Commission's General Rules of Practice (49 CFR §1100.247) and include a concise statement of protestant's interest in the proceeding and copies of its conflicting statements in the record. 'A copy of the protest shall be served concurrently upon applicant's representative, or if no representative is named.

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October 12, 1976. Such protests shall comply with Special Rule 247(d) of the Commission's General Rules of Practice (49 CFR §1100.247) and include a concise statement of protestant's interest in the proceeding and copies of its conflicting statements in the record. 'A copy of the protest shall be served concurrently upon applicant's representative, or if no representative is named.

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Each protest shall be served on the Commission, a copy of which shall be sent to each applicant.

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Each protest shall state the time at which and the place where the protestant will be present, if any.

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Motor Carrier Alternate Route

Deviations

The following letter-notices to operate over deviation routes for operating convenience only have been filed with the Commission under the Commission's Deviation Rules-Motor Carriers of Property (49 CFR § 1042.4(a) (11)).

Motor Carriers of Property

No. MC 1515 (Deviation No. 712) (Cancels Deviation No. 677), GREYHOUND LINES, INC., Greyhound Tower, Phoenix, Ariz., 85007, filed August 18, 1976. Carrier proposes to operate as a common carrier, by motor vehicle, of passengers and their baggage, and express and newspapers in the same vehicle with passengers, over deviation routes as follows: From Chicago, Ill., over Interstate Highway 90 to Junction Illinois Highway 5, thence over Illinois Highway 5 to Junction Illinois Highway 10, thence east over Illinois Highway 92, with the following access routes: (1) From Junction Illinois Highway 5 and DeKalb East Road, DeKalb East Road to Junction Illinois Highway 5; (2) From Junction Illinois Highway 5 and Anne Glidden Road, Anne Glidden Road to Junction Illinois Highway 5; (3) From Junction Illinois Highway 78 and Illinois Highway 5 to Junction Illinois Highway 78; (4) Between Marion, Ill., and Seguin, Tex., serving all intermediate points; from Marion over U.S. Highway 183 and U.S. Highway 90-A for purposes of joinder: From Luling over U.S. Highway 183 to Gonzales and return over the same route; (5) Between Luling, Tex., and Gonzales, Tex., serving all intermediate points and serving the junction of U.S. Highway 183 and U.S. Highway 90-A over U.S. Highway 90-A to Seguin, Tex., and return, and joining, tacking and coordinating the authority described above with authority presently contained in Common Carrier Certificate No. 2892, Intrastate, interstate and foreign commerce authority sought.

Hearing.—Date, time and place will be assigned for a hearing approximately 30 days after publication in the Federal Register. Requests for procedural information should be addressed to the Transportation Division, Railroad Commission of Texas, P.O. Drawer 12967, Austin, Tex. 78711. If needed, the proceeding may be extended.

By the Commission.

H. G. Hoyme, Jr.,
Acting Secretary.

PETITION OF HERMAN BROS., INC., FOR THE INSTITUTION OF RULEMAKING PROCEEDINGS

September 2, 1976.

Notice to all parties: At the request of Fritz K. Kahn, representative for Herman Bros., Inc., the time for filing comments in the above-entitled proceeding has been extended from September 22, 1976, to November 22, 1976. No further extensions.

H. Gordon Hoyme, Jr.,
Acting Secretary.

NOTICES
PART II:

DEPARTMENT OF
HEALTH,
EDUCATION, AND
WELFARE

Food and Drug Administration

OVER-THE-COUNTER
DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products
OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antihistaminic Products

The Food and Drug Administration (FDA) proposes to establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator and antihistaminic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antihistaminic Products.

In accordance with § 330.10(a) (2) (21 CFR 330.10(a) (2)), all data and information concerning each drug, allergy, bronchodilator and antihistaminic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All information which would be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before October 15, 1975, to which a person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(3) of the Federal Food, Drug, and Cosmetic Act is to remain confidential. To protect confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commission proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and not misbranded, or as Category II-drugs, be permitted to remain in use at a dosage level lower than that recommended by the Panel.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective or would result in misbranding, be reclassified for not longer than 2 to 5 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the Federal Register.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—safe and effective or would result in misbranding, be permitted to remain in use for not longer than 2 to 5 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the Federal Register, regardless whether further testing is undertaken to justify their future use.

The purpose of this preamble is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made regarding the monograph of the Panel. The report of the Panel represents the best scientific judgment of the members. The report has been prepared for FDA, but it does not necessarily reflect the agency position on any particular matter contained therein.

After a careful review of all comments submitted in response to this proposal, the final monograph will include a tentative final regulation in the Federal Register to establish a monograph for OTC cold, cough, allergy, bronchodilator and antihistaminic drug products.

The Food and Drug Administration (FDA) proposes to establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator and antihistaminic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antihistaminic Products.

Proper distribution is required to establish the OTC cold, cough, allergy, bronchodilator, and antihistaminic drug products from prescription use prior to the finalization of an applicable monograph for the ingredients. The reclassification of ingredients in the OTC Advisory Panel report presents important issues that need careful and special consideration.

Accordingly, the Commissioner proposed, in the Press Release of December 4, 1975 (40 FR 56675), a policy to clarify the marketing status of (1) all ingredients currently restricted to prescription use which an OTC advisory panel recommends as Category I (safe and effective), Category II (not safe and effective), or Category III (the available data are insufficient to classify the drug); and (2) the use of active ingredients at dosage levels higher than that available in any OTC drug product.

The Commissioner also advised in the preamble to the proposal in the December 4, 1975 Federal Register that he may indicate his disagreement with the panel's recommendation(s) regarding specific ingredients proposed for Category III classification.

The Commissioner has reviewed those recommendations that are currently limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. He has made an initial determination that an approved NDA is required for OTC marketing of promethazine for any indication, for OTC marketing of doxylamine succinate as an antihistamine at a dosage level in excess of 7.75 mg (2.5 mg per tablet), and for OTC marketing of diphenhydramine as an antihistamine. The Commissioner is deferring his decision on the Panel's recommendation that diphenhydramine be reclassified for general recognition as safe and effective for OTC use as an antihistamine until the agency has had an opportunity to rule on a supplemental NDA now pending for OTC use of an antipruritic product containing diphenhydramine.

The Commissioner has made an initial determination that an approved NDA is required for OTC marketing of diphenhydramine for any indication, for OTC marketing of doxylamine succinate as an antihistamine at a dosage level in excess of 7.75 mg (2.5 mg per tablet), and for OTC marketing of promethazine as an antihistamine. The Commissioner has deferred his decision on the Panel's recommendation that promethazine be reclassified for general recognition as safe and effective for OTC use as an antihistamine until the agency has had an opportunity to rule on a supplemental NDA now pending for OTC use of an antipruritic product containing diphenhydramine.

Promethazine. The Panel recommended classification of the ingredient promethazine as Category I in the OTC antihistaminic drug. This ingredient is presently a component of drug products that are the subject of approved NDA's for prescription use as antihistamines.
sedatives, as antihistamines, as adjuvants with narcotics for preoperative sedation, and in the postoperative management of pain. *Promethazine* is the only antihistaminic drug reviewed by the Panel that is chemically identified as a phenothiazine derivative; no ingredients in this class are currently available for OTC use. *Promethazine*, like other phenothiazines, is known to produce certain serious adverse effects, including agranulocytosis, thrombocytopenia, hypoplastic anemia, extrapyramidal symptoms, and hypotension (*AMA Drug Evaluations, p. 497*); although it may produce these effects less frequently than do other phenothiazines. Although these adverse effects are of considerable concern, the major consideration relates to the effects of promethazine on the central nervous system (CNS). *Promethazine* is known to have a hypnotic effect more conspicuous than that of the other antihistamines (see Krantz and Carr, *The Pharmacologic Principles of Medical Practice, 8th Ed., p. 818*), not noted in the proposal regarding a high incidence of drowsiness compared to other antihistaminic agents of the ethanolamine class of antihistamines. *Promethazine* is noted for its hypnotic effect more so than any other antihistaminic agent, especially in children. Children also seem particularly liable to develop such CNS adverse reactions of the awake, in sensorium, evidence of extrapyramidal disturbances, convulsions, and, rarely, coma and death. The Commissioner notes that the marketing status of *Promethazine* as an antihistaminic is independent of his decision on its status as an antitussive, although, obviously, some of the underlying factual considerations are common to each.

*Doxylamine succinate.* The Panel recommended classification of the ingredient doxylamine succinate as a Category I OTC antihistamine drug at the 7.5 to 12.5 mg dosage level. This ingredient is an approved NDA for prescription use, and for OTC use at the 7.5 mg dosage level, for several indications, including the management of perennial and seasonal rhinitis, and nasal congestion due to vasomotor rhinitis pursuant to the requirements of § 310.201(a)(13) (21 CFR 310.201(a)(13)). The Commissioner concludes that doxylamine succinate should continue to be classified as a new drug and a prescription drug at dosage levels in excess of 7.5 mg. The Commissioner notes that the Panel has determined that doxylamine succinate should not be approved for OTC use. The Commissioner has concluded that the marketing status of diphenhydramine hydrochloride as an antitussive should be resolved by first considering the approval status of this supplemental NDA. He has determined that, at this time, the Commissioner is concerned that consumers accustomed to purchasing a particular product may not be aware of the increased amount of active ingredient per dosage unit. The Commissioner concludes that consumers should be fully informed about the increased dosage. He has determined, however, that he believes that it is in the best interest of the public to allow the NDA to be approved and allow the NDA to be approved and elect to reformulate their marketed products shall clearly indicate any increased dosage level on the principal display panel of each product. He further recommends that, in the case of tablet formulations, scored tablets be available to assist the consumer in achieving a lower dosage, if one is desired.

The Commissioner notes that the marketing status of diphenhydramine hydrochloride as an antitussive is different from issues surrounding its OTC use as an antitussive. The indications, dosage levels, and number of available effective alternatives are different when comparing these dosage levels. Diphenhydramine hydrochloride is the active ingredient in several products with approved NDA's. All such products are limited to prescription use. The Panel recommended that diphenhydramine hydrochloride be classified in Category I for antitussive use at 25 to 50 mg, which is the usual prescription dosage level. Diphenhydramine hydrochloride, like doxylamine succinate, is a member of the ethanolamine class of antihistamines. If, too, has a pronounced tendency to produce sedation in a high proportion of those persons who take it (*AMA Drug Evaluations, p. 493*). For this reason, the Commissioner concludes that diphenhydramine hydrochloride should remain a prescription new drug ingredient and not be available for use as an antihistaminic. The diphenhydramine hydrochloride product is currently marketed OTC as an antihistaminic at any dosage level.

The Panel also recommended that diphenhydramine hydrochloride be classified in Category I for OTC use as an antitussive. Diphenhydramine hydrochloride is the active ingredient in a cough syrup now being marketed OTC. The currently effective NDA for this product limits it to prescription use and labels it as an expectorant only. The holder of the NDA has submitted a supplemental NDA that contains data in support of a claim that the product is safe and effective for use as an antitussive. The supplemental NDA also requests that the product be approved for OTC use. The Commissioner has concluded that the marketing status of diphenhydramine hydrochloride as an antitussive should be resolved by first considering the approval status of this supplemental NDA. He has determined that, at this time, the Commissioner is concerned that consumers accustomed to purchasing a particular product may not be aware of the increased amount of active ingredient per dosage unit. The Commissioner concludes that consumers should be fully informed about the increased dosage. He has determined, however, that he believes that it is in the best interest of the public to allow the NDA to be approved and allow the NDA to be approved and elect to reformulate their marketed products shall clearly indicate any increased dosage level on the principal display panel of each product. He further recommends that, in the case of tablet formulations, scored tablets be available to assist the consumer in achieving a lower dosage, if one is desired.

The Commissioner further recommended that theophylline and methoxyphephrine be made available OTC as single ingredients. The Commissioner does not contest the judgment of the Panel regarding the safety of these ingredients. However, he points out that he believes there is a scientific issue whether the recommended dosage levels are therapeutically effective for a significant identifiable population of asthmatics. Therefore, these two ingredients are currently undergoing extensive review within the agency. Consequently, the decision of the Panel may be subject to modification in the tentative final monograph.

The Commissioner invites full public comment on all of the conclusions and recommendations made in this proposed rule.
recommendations of the Panel, and on his own specific conclusions regarding pseudoephedrine, diphenhydramine, chlorpheniramine, pseudophedrine, theophylline, and methylophenamine. The Commissioner has reviewed the potential commerce of the recommendations and proposed monograph of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antihistaminic Products and has concluded that the Panel's recommendations and proposed monograph will not significantly affect the quality of the human environment and that an environmental impact statement is not required. The Commissioner has also considered the inflation impact of the Panel's recommendations and proposed monograph, and no major inflation impact has been found, as defined in Executive Order 11821, OMB Circular A-101, and the Guidelines issued by the Department of Health, Education, and Welfare. Copies of the environmental and inflation impact assessments are on file with the Office of Hearings, Food and Drug Administration, Rm. 4-65, 5000 Fishers Lane, Rockville, MD 20852.

The conclusions and recommendations in the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antihistaminic Products follow:

In the Federal Register of January 5, 1972 (37 FR 38), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. On May 3, 1972, the Commissioner signed the final regulations providing for the OTC drug review under §330.10 published in the Federal Register of May 11, 1972 (37 FR 8424), which were made effective immediately. Pursuant to these regulations the Commissioner issued a request for data and information on all cold, cough, allergy, bronchodilator and antihistaminic (CCABA) active ingredients in drug products, in the Federal Register of August 9, 1972 (37 FR 16029).

The Commissioner appointed the following panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC cold, cough, allergy, bronchodilator, and antihistaminic ingredients pursuant to §330.10(a)(1):

- Francis B. Lovell, M.D., Chairman
- Hylan A. Blackman, M.D.
- Hella Brown, M.D.
- Robert E. Chemers, Ph.D.
- Mary Jo Reilly, M.S.
- James R. Turemen, M.D.
- Colin B. Woolf, M.D.

The panel was first convened on November 9, 1972, in an organizational meeting. Working meetings were held on December 11 and 12, 1972; January 23 and 24, February 28 and March 1, April 5 and 6, May 10 and 11, June 9 and 30, September 23 and 26, October 31 and November 1, December 6 and 7, 1973; January 5, March 30 and 31, June 12 and 13, September 12 and 12, October 31, November 1, December 2 and 4, 1974; January 30 and 31, April 3, 4 and 5, May 23 and 26, July 17 and 18, September 24, November 29, 30, 20 and 21, and December 18, 19 and 19, 1975; February 2, and March 2 and 4, 1976.

Two nonvoting liaison representatives served on the panel. Mrs. Anita Dihlhauser, nominated by an ad hoc group of consumer organizations, served as the consumer liaison and Joseph L. Kegly, Ph.D., nominated by the Proprietary Association, served as the industry liaison.

The following employees of the Food and Drug Administration served: Anna L. Standard, M.D., Executive Secretary until March 26, 1974, followed by Joel Aronson, Ph.D.; Thomas D. DeChillis, Ph.D., Panel Administrator; Recie Bomar, Ph.D., Drug Information Analyst until February 10, 1973, followed by Lloyd G. Scott, Ph.D. until May, 1974, followed by Gary P. Troskel, Ph.D.

In addition to the Panel members and liaison representatives, the following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request:

- Paul Bass, Ph.D.
- C. Warren Bearman, M.D.
- John Beberman, M.D.
- Richard C. Droge, Ph.D.
- C. Edward Buckley, M.D.
- John C. Oates, Jr., Ph.D.
- Robert E. Choate
- Sanford Chodosh, M.D.
- John T. Connell, M.D.
- Joseph Dresner
- Constantine Faullini, M.D.
- Arthur D. Flemington, M.D.
- Spencer E. Eto, Ph.D.
- Arthur Grollman, D.D.
- Robert M. Hodges
- Robert F. Hurdle, Sc.D.
- Clarence Imboden, M.D.
- Charles Janeway, M.D.
- Anita John, Ph.D.
- Stuart J. Land, Esq.
- Ben Marc Lamann, M.D.
- Vincent D. Martin, M.D.
- Eugene G. Tanarelli, M.D.
- Jennifer Trampel, M.D.
- J. L. London, M.D.
- Leslie M. Lucas, M.D.
- Guillermo Martinez
- John McMeans, M.D.
- Fletcherson, M.D.
- Eilas W. Parkman, Sc.D.
- Joseph Pappas, Esq.
- Joseph J. Phifer, M.D.
- William R. Poff
- Thomas W. Richards, M.D.
- Norman Tidball, Ph.D.
- Robert T. Scammon, M.D.
- Daniel L. Shaw, Jr., M.D.
- Alex Silverman, M.D.
- Joseph Smith, M.D.
- Alfred E. Sutherland, Esq.
- William W. Swenson, Esq.
- M. L. Thierman, M.D.
- Sumner Yaffe, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submitted to interested parties, and has considered all pertinent data and information submitted through March 3, 1976 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

Category I. Conditions under which cold, cough, allergy, bronchodilator and antihistaminic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which cold, cough, allergy, bronchodilator and antihistaminic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends the following for each group of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the Federal Register.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the Federal Register, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded; or as Category II not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for a period of time justified in the report of 2, 3, 4 or 5 years for the specific conditions after the date of publication of the final monograph in the Federal Register, at the discretion of or distributor of any such drug utilizing such conditions. In the interim panels tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.
Pursuant to the notice published in the Federal Register of August 9, 1972 (37 FR 16029) requesting the submission of data and information on cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) drugs, the following firms made submissions relating to the indicated products:

### A. Submissions by Firms

<table>
<thead>
<tr>
<th>Firm</th>
<th>Marketed Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. <strong>Abbott Laboratories</strong>, North Chicago, Ill. 60064.</td>
<td>Cyleclidine Syrup, Quelldrine Cough Syrup.</td>
</tr>
<tr>
<td>Block Drug Co., Inc., Jersey City, N.J. 07302.</td>
<td>BC All Clear.</td>
</tr>
<tr>
<td>Cheesbrough-Pond's, Inc., Trumbull, Conn. 06611.</td>
<td>Cold-Team-24 Daytime Tablets, Cold-Team-Nighttime Liquid, Pertussin 8-Hour Cough Formula, Pertussin Medicated Vaportizer, Pertussin Plus Night-Time Cold Medicine, Pertussin Wild Berry Cough Syrup.</td>
</tr>
<tr>
<td>Cremeulsion Co., Atlanta, Ga. 30301.</td>
<td>Cough Chek, Cotechel, Cremeulsion Cough Medicine, Cremeulsion Cough Medicine for Children, C creoets Cough and Throat Lozenges.</td>
</tr>
<tr>
<td>Dorsey Laboratories, Lincoln, Nebr. 68501.</td>
<td>Chexit Tablets, Dor-O Tablets, Dorcol Pediatric Cough Syrup, Triaminic Expectorant, Triaminic Syrup, Triaminic Nasal spray, Triaminic Tablets, Triaminic Cough Syrup, Tussagesic Suspension, Tussagesic Tablets, and Ursalin Tablets.</td>
</tr>
<tr>
<td>D. <strong>The Dow Chemical Co.</strong>, Zionsville, Ind. 46077.</td>
<td>Novahlstine DH, Novahlstine Elixir, Novahlstine Expectorant, Novahlstine Fortis Capsules, Novahlstine Melet Tablets, 2/0, and 2G/DM.</td>
</tr>
<tr>
<td>Hall Brothers, Radcliffe, Manchester England.</td>
<td>Hall's Cherry Cough Drops.</td>
</tr>
<tr>
<td>Key Pharmaceuticals, Inc., Miami, Fla. 33160.</td>
<td>Verequad Suspension, Verequad Tablets.</td>
</tr>
<tr>
<td>Miles Laboratories, Inc., Elkhardt, Ind. 46514.</td>
<td>Methyprylon Pumarate, Methyprylon Hydrochloride.</td>
</tr>
<tr>
<td>Monsanto Co., St. Louis, Mo. 63166.</td>
<td>Co-Tylenol Cold Formula.</td>
</tr>
</tbody>
</table>

Norwich Products, Norwich, N.Y. 13815.

Parke-Davis & Co., Detroit, Mich. 48232.


Pfizer Pharmaceuticals, New York, N.Y. 10017.

Pharmacists, Rochester, N.Y. 14603.

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Pharmacists, Rochester, N.Y. 14603.
PROPOSED RULES

33371


Bed intravenous solutions.

Listerine Big & Cough Formula, Hall's Mentho-Lyptus Cough Tablets, Listerine Antiseptic, Listerine Antiseptic throat lozenges, Listerine Antiseptic throat lozenges (orange), Listerine Cold Cough Control lozenges, Smith Brothers Medicated Cough Drops (black licorice), Smith Brothers Medicated Cough Drops with Benzocaine (mixed menthol), Smith Brothers Medicated Cough Drops (Wild Cherry), Super Analgesic Decongestant Tablets, Super Analgesic Decongestant Nasal Spray.


Bronitin Tablets, Bronitin Mist, Clear & Dry Sialus Clearant Tablets, Dorrind Antiseptic Tablets, Dristan Decongestant Tablets, Dristan Capsules, Dristan Nasal Mist, Dristan Decongestant Vapor Nasal Spray, Primatene II Formula Tablets, Primatene Mist, Primatene P Formula Tablets, Dristan Decongestant Cough Formula.

Wyeth Laboratories, Philadelphia, Pa., 19101.

Phenergan.

Wyeth Laboratories, Philadelphia, Pa., 19101.

In addition, the following firms or groups make related submissions:

Firm | Submissions
--- | ---
Bristol-Myers Products, New York, N.Y., 10022. | Phenylephrine hydrochloride, Phenylpropanolamine, Theophylline sodium glycolate,

Miles Laboratories, Inc., Elkhart, Ind., 46514. | Methyprylon hydrochloride.

Parke Davis & Co., Detroit, Mich., 48223. | Phenylpropanolamine salt.


Linda Tallaferro, Austin, Tex., 78712. | Promethazine hydrochloride.


Vick Division Research, Mount Vernon, N.Y., 10553. | Promethazine hydrochloride.


N. Labeled ingredients contained in medicinal products submitted to the panel

Acetaminophen (N-acetyl-p-aminophenol)
Acetanilide
Acetic acid
N-acetyl-p-aminophenol (acetaminophen)
Alcohol
Alkyldimethyl benzylammonium chloride (benzalkonium chloride)
Alum
Alumina hydroxide-magnesium carbonate co-crystallized gel
1. **Active ingredients.** The Panel has classified the following ingredients submitted to the Panel into groups identified below:

### ACTIVITIES

- **Antitussives**
  - Caramiphen ethanesulfonate (caramiphen ethanesulfonate)
  - Caramiphen ethanesulfonate (caramiphen ethanesulfonate)
  - Caramiphen ethanesulfonate (caramiphen ethanesulfonate)
  - Caramiphen ethanesulfonate (caramiphen ethanesulfonate)

- **Antihistamines**
  - Brompheniramine maleate
  - Chlorpheniramine maleate
  - Diphenhydramine hydrochloride
  - Doxylamine succinate
  - Methapyrilene hydrochloride
  - Methapyrilene hydrochloride
  - Phenindamine tartrate
  - Phenylpropanolamine citrate
  - Promethazine hydrochloride

- **Bronchodilators**
  - Theophylline
  - Theophylline
  - Theophylline
  - Theophylline

- **Expectorants**
  - Ammonium chloride
  - Antimonium potassium tartrate
  - Beechwood creosote

- **Miscellaneous labeled ingredients:**
  - Antihistamines with sleep-aid claims
  - Ascorbic acid (vitamin C)
  - Caffeine
  - Phenobarbital
  - Vitamins

2. **Ingredients reviewed by the Panel in addition to the submitted data:**

### SYMPATHOMIMETIC AMINES

- Belladonna alkaloids
  - Ephetrine
  - Ephetrine hydrochloride
  - Ephetrine sulfate

### DOPAMINERGIC AGENTS

- Amphetamine
  - Diphenhydramine hydrochloride

### MISCELLANEOUS

- Euphorbia pluifera
PROPOSED RULES

The OTC cold, cough, allergy, bronchodilator and antihistaminic Panel was charged with the review and the evaluation of safety and effectiveness of those cold, cough, allergy, bronchodilator, and antihistaminic ingredients and combinations thereof, the adequacy of their labeling, and to advise the Commissioner of Food and Drugs on the promulgation of monographs establishing conditions under which these over-the-counter (OTC) drug products are generally recognized as safe and effective and not misbranded. The Panel also served as a forum for the exchange of views regarding the prescription or nonprescription status of these various active ingredients and combinations thereof. The panel members were expected to call upon their own expert knowledge and experience in carrying out each element of this charge. Specifically, the Panel was charged with the following:

1. Review and evaluation of all data made available to the panel members concerning the safety and effectiveness of cold, cough, allergy, bronchodilator and antihistaminic treatment and prevention agents, and combinations thereof, utilized in these OTC drug products.

2. Advising the Food and Drug Administration as to the adequacy of the labeling of such cold, cough, allergy, bronchodilator and antihistaminic treatment and prevention drug products and to make recommendations as to the contents of future labeling of such products.

3. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which, based upon the available data, could be considered safe and effective for the above stated uses. These recommendations must be in keeping with agency stated definitions of the terms "safe" and "effective" and in keeping with the agency OTC drug combination policy (21 CFR 330.10(a) (i)).

4. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which, based upon the available data, are not considered as safe and effective for the above stated uses. The same criteria must apply as in the determinations of those ingredients which are found to be safe and effective.

5. Advising the Food and Drug Administration regarding those ingredients which in the judgment are likely to be safe and effective, but for which more data are needed. In such cases the Panel was requested to give some guidance as to what type of studies and the maximum time period they feel would be adequate to produce such information for future consideration by the Food and Drug Administration.

6. Advising the Food and Drug Administration on the promulgation of a monograph or monographs establishing conditions under which these OTC drug products are generally recognized as safe and effective and not misbranded. This information is submitted as part of a written report by the Panel containing the following basic recommendations:

a. A statement of the acceptable indications for use.

b. Recommended labeling guidelines—warnings, precautions, contraindications, directions for use.

c. A statement of the acceptable indications for use.

b. DISEASES AND RELATED SYMPTOMS RELIEVED BY OTC COLD, COUGH, BRONCHODILATOR AND ANTIHISTAMINIC PRODUCTS

The Panel makes the following statements and recommendations concerning the symptoms related to the use of antitusives, expectorants, bronchodilators, anticholinergics, and nasal decongestants. The symptoms which these drugs may be expected to relieve are those occurring in certain allergic states such as hay fevers, asthma, and symptoms in the nose, eyes, sinuses and throat caused by the common cold and other mild respiratory infections. It must be kept in mind that the ingredients and combinations reviewed are not intended to cure but are OTC drugs to provide symptomatic relief.

The Panel has prepared the following table which lists symptoms and the acceptable corresponding pharmacologic groups of drugs for the treatment of these symptoms:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Acceptable Pharmacologic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold</td>
<td>Antihistamines, decongestants</td>
</tr>
<tr>
<td>Cough</td>
<td>Bronchodilators, mucolytics</td>
</tr>
<tr>
<td>Allergy</td>
<td>Antihistamines, decongestants</td>
</tr>
<tr>
<td>Bronchodilation</td>
<td>Bronchodilators, anticholinergics</td>
</tr>
<tr>
<td>Antihistaminic</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Nasal Decongestion</td>
<td>Nasal decongestants</td>
</tr>
</tbody>
</table>

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### Symptom

1. **Bronchospasm or asthma**

   **Pharmacologic group**
   Bronchodilators (sympathomimetic amines, theophyllines)—with the Category I labeling indications recommended by the Panel. (See pt. V, par. B.I. below—Labeling.)

2. **Cough**

   **Antitussives**—with the Category I labeling indications recommended by the Panel. (See pt. III, par. B.I. below—Labeling.)

3. **Runny nose**

   **Anticholinergics**—with the Category I labeling indications recommended by the Panel. (See pt. IV, par. B.I. below—Labeling.)

4. **Nasal congestion**

   **Antihistamines**—with the Category I labeling indications recommended by the Panel. (See pt. VII, par. B.I. below—Labeling.)

5. **Sinus congestion**

   **Analgesics**—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.

6. **Sneezing, watery eyes, and itchy eyes**

   **Antihistamines**—with the Category I labeling indications recommended by the Panel. (See pt. VII, par. B.I. below—Labeling.)

7. **Sore throat**

   **Analgesics**—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.

8. **Generalized aching**

   **Antipyretics**—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.

9. **Fever**

   **Antipyretics**—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.

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1. **Allergy.** Allergy is a complex of symptoms which arises under circumstances when a person who has acquired a hypersensitivity to a substance encounters that substance. Although one may be born with a tendency to become allergic, one must be exposed to a substance for weeks, months or years before one actually becomes allergic to it. Probably about 15 percent or more of the population becomes significantly allergic. Substances to which people ordinarily become allergic are pollens, mold spores, animal dander and certain dusts and sprays in the home and in industry. These are airborne and are inhaled. One may also become allergic to certain foods and drugs and to substances coming in contact with the skin such as drugs and poison ivy (poison oak). Substances to which people become allergic are called allergens. In our highly industrial and technological society we are increasingly exposed to allergens never encountered by our forebears; for this reason, the number of persons with allergies is rising and may continue to rise.

The allergic symptoms with which the Panel is concerned are nasal (sneezing, watery or mucous discharge, itching and obstruction), and bronchial (cough, bronchospasm and expectoration). Another manifestation of allergy is itchy and watery eyes. Allergy of this type belongs to a subgroup of the so-called "immunoglobulin" class of disease termed "asthma." In this class of disease an antibody mediates the reaction. The antibody belongs to the IgE class of immunoglobulins which has the peculiarity of attaching itself to a certain type of cell (mast cells in the tissues and basophils in the blood). With the arrival of the allergen, union between the allergen and the antibody attached to these cells occurs and leads to the release of substances which in turn cause the symptoms we call "allergy." One of the substances released, and probably the principal one, is histamine. The antihistaminic drugs block the action of histamine.

Identification and elimination of the offending substance (allergen) are the measures of choice. However, these are often impossible to achieve. The proper use of OTC products containing antihistamines, sympathomimetics, or theophyllines may provide relief of allergy symptoms. Although OTC drugs are often adequate for relief, the allergic reaction may be so intense that OTC drugs are not adequate and other measures, such as epinephrine by injection, and corticosteroids, requiring the supervision of a physician are needed. In the case of allergy to pollens and other inhaled allergens, symptoms can be lessened or eliminated under medical supervision by a course of injections of suitably prepared allergenic extract.

### References


### Medications

**Analgesics**
- Acetaminophen
- Aspirin
- Sulfinpyrazone

**Antihistamines**
- Cetirizine
- Chlorpheniramine
- Diphenhydramine
- Fexofenadine
- Levocetirizine
- Loratadine
- Mepyramine
- Tofacitinib
- Terfenadine
- Triprolidine

**Anticholinergics**
- Atropine
- Benztropine
- Propantheline

**Antipyretics**
- Acetaminophen
- Nimesulide

**Local anesthetics**
- Benzocaine

**Oral Cavity Panel**
- Doxycycline

**Pharmacologic group**

- Bronchodilators
- NSAID

**Analgesic Panel**
- Acetaminophen
- Ibuprofen
- Naproxen

**Internal Analgesic Panel**
- Acetaminophen
- Ibuprofen
- Naproxen

**Oxygen**
- Oxygen

### Asthma and Other Respiratory Diseases and the Use of Bronchodilators

Asthma is a disease in which there is widespread narrowing of the airways due to airway wall muscle spasm which occurs in response to various stimuli. Among the stimuli which may lead to asthma is the inhalation of substances such as pollens and animal dander in people who are allergic to these substances. This reaction causes partial obstruction to air flow and shortness of breath. The spasm under the mucosa of the air tubes may subside either spontaneously or as a result of therapy. Airway narrowing occurs also where there is widespread bronchial infection such as in acute or chronic bronchitis, in pulmonary emphysema where there is destruction of the lung tissue, and in pulmonary congestion from failure of the left side of the heart. Asthma is a difficult disease condition for the layman to diagnose and even physicians have difficulty in distinguishing asthma from the above other conditions which cause airway narrowing. Therefore, it is very important that the diagnosis of asthma be established by a physician before the use of OTC bronchodilator preparations.

Medications which relax the airway muscle spasm and relieve the shortness of breath of asthma are called bronchodilators. Usually these drugs are given by mouth as a tablet or liquid, or they may be inhaled as a spray from a suitable dispenser. The response of mild or even moderate asthma to these drugs is often quick and there is effective relief from shortness of breath. The Panel believes that, when taken as directed, the drugs are safe for OTC use, but undesirable effects can occur. These adverse effects are mainly exhibited as increased rate and force of the heart beat, rise in blood pressure, nervousness and sleeplessness, and nausea or vomiting.

Asthma is a very common disease and it is reasonable to have bronchodilators available on a nonprescription basis so that in mild cases relief may be obtained quickly without the possible delays of obtaining a physician's prescription. However, it is very important that the diagnosis of asthma first be established by a physician as some of the other conditions which resemble asthma, such as pulmonary congestion from failure of the left side of the heart, should not be treated by certain types of bronchodilators. Even the patient with true asthma should be warned that if a bronchodilator does not cause excellent and rapid relief, he should call his physician. The reason he should call his physician is that in a severe and worsening attack of asthma, slight relief may be given by these bronchodilators and this may give a false sense of security. The patient may then postpone seeking medical help or going to a hospital until his disease has reached life-threatening severity. Therefore, labeling of these preparations should be very precise in that the patient should be instructed to seek medical assistance immediately if relief of his symptoms does not occur within a short time of us-
...ing the bronchodilator preparation. In the use of ephedrine aerosol, relief should occur within 20 minutes; in the use of tablets and tablets of theophylline and its salts, relief should occur within 1 hour.

References


3. "The common cold." (cold). The "common cold" (cold) is a self-limited respiratory infection caused by one or more viruses. A cold is rarely serious and is readily transmitted. Throughout this document, the Panel has used the term "common cold" which the Panel considers synonymous with the term "cold."

A "common cold" often begins quite abruptly with sneezing, runny nose, sore throat, cough, and fatigue. The discharge, followed by nasal congestion. The discharge may subsequently become mucoid or purulent. After the first day or two, the eyes may become suffused and the voice husky. The nasal congestion intensifies and the sense of smell and taste is often suppressed or absent. Extension into the sinuses may be described in the rhinitis statement. Lethargy, some aches and pains and slight fever may be present. The course is variable and may extend for 7 to 14 days. Cough may occur, especially in the later stages.

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Early in its course, the cold is indistinguishable from the early stages of measles, rubella, chickenpox, pertussis, cerebrospinal fever, influenza and atypical pneumonia. The cold also closely simulates allergic rhinitis. The physician's main role in the cold is to exclude more serious illness.

There is no generally accepted treatment that can prevent, cure or shorten the course of the "common cold." Treatments which are available only relieve symptoms. A symptomatic course may be short, especially because many individuals have one to three colds each year.

Cough. A cough is the rapid expulsion of air at high velocity from the respiratory airway producing a noise of varying pitch and intensity. Impulses that initiate the cough reflex may arise from many areas within and outside the respiratory tract.

Normally, coughing is produced by stimulation of the sensory endings of the glossopharyngeal and vagus nerves within the mucous membranes of the respiratory tract. This stimulation can be initiated by infection, chemical irritation, the presence of retained secretions, or foreign material blocking the breathing passages. Localized narrowing of the air passages may play an important role in stimulation of the cough reflex. Cough can also occur from stimulation outside the respiratory tract. For example, if the external ear is tickled, a cough is produced. Cough can be under considerable voluntary control and therefore can be self-suppressed to a degree. Likewise, an individual can initiate cough at will. Cough can cause unhealthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material.

Medications which suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. These preparations are administered by mouth to the four cardinal types of cough, such as codeine and hydrocodone, commonly cause constipation as a side effect.

The cough is a protective, physiological reflex occurring in healthy as well as diseased individuals. It is frequently the presenting symptom in a wide variety of conditions, such as colds, bronchitis, or mild, self-limiting illness to a serious and even fatal disease. In certain disease states such as asthma, chronic bronchitis and cystic fibrosis, the cough reflex is essential in maintaining an open airway by clearing the respiratory passages of excessive secretions. Because of its importance in preserving the function of the lung, the cough reflex should not be suppressed indiscriminately.

The irritative cough associated with a self-limiting respiratory tract infection is usually viral in nature or follows the inhalation of irritating gases or dusts, and can readily be recognized and serves no useful function. These conditions are usually associated with a dry, hacking, nonproductive cough. In which no expectoration is expectorated and lends itself to the diagnosis of allergic rhinitis contains such a large number of eosinophils. The discharge is usually viral in nature or follows the inhalation of irritating gases or dusts, and can readily be recognized and serves no useful function. These conditions are usually associated with a dry, hacking, nonproductive cough which may persist for longer than 1 week should be investigated by a physician to exclude the presence of an underlying, potentially serious, respiratory disease.

Symptoms of sinus congestion. Nasal stuffiness is mucous membrane-lined air cavities in the bony structure of the skull which are continuous with the nasal cavity. Impaired sinus drainage due to nasal congestion, e.g., rhinitis of upper respiratory infection or nasal allergy, may result in sinus inflammation (sinoitis) with associated headache and facial pain or tenderness in the region of the affected sinus(es).

Self-medication with an oral or topical medication may aid in resolving the problem by diminishing the nasal obstruction which impairs sinus drainage. An orally administered analgesic, e.g., aspirin, acetaminophen, should provide symptomatic relief from headache and pain associated with the sinus congestion. If symptoms persist, intensity of discomfort increases or if fever, a physician should be consulted.

6. Rhinitis (allergic rhinitis, vasomotor rhinitis). a. Allergic rhinitis. Allergic rhinitis is caused by allergy to airborne allergens including pollens, animal danders, molds and dust is described elsewhere in this document. (See part II paragraph 5.1 above—Allergy.)

The symptoms of rhinitis are sneezing, watery discharge from the nose, nasal stuffiness and obstruction and nasal itching. The eyes may also be involved in which case they then itching, tearing or redness. There may also be puffedness of the eyelids. Less frequently there is headache, itching of the throat and ears and there may be cough. A frequent associated symptom is swelling of the tissues with a feeling of pressure or a feeling of fullness. In this case, the nasal cavity is obstructed and is difficult to breathe. The nasal discharge may be watery or clear.

In addition to rhinitis the nasal sinususes are frequently involved. This may cause headache usually frontal in distribution or pain or discomfort in the frontal, ethmoid, maxillary or antral sinuses in the front of the face surrounding the nose.

Sneezing may occur irregularly or in paroxysms, more commonly on awakening or in the morning, or may be caused by such nonspecific factors as exposure to abrupt changes in temperature or inhalation of particulate matter.

The nasal discharge may be watery in nature or mucoid or purulent. In one or safe at the dosages recommended for adults or children. rhinitis is caused by foreign material blocking the breathing of the affected sinus(es).

For example, if the age is 1 year, an orally administered analgesic, little or no seasonal variation. The condition is usually called vasomotor rhinitis suggesting an abnormal reactivity of the
blood vessels in the nasal lining but in fact the reason for symptoms is unknown. The symptoms of vasomotor rhinitis are the same as those for allergic rhinitis. Skin tests are not helpful in diagnosis.

c. Treatment of rhinitis symptoms. The antihistamines are most effective in the treatment of mild allergic rhinitis (such as hay fever). They are less effective in vasomotor rhinitis. These drugs are discussed more completely later in this document. (See part VII, below—Antihistamines.) Nasal decongestants and anticholinergics have also been used in the management of the symptoms of rhinitis. The use of these drugs will be discussed more completely later in this document. (See part VI, below—Anticholinergics and part VIII, below—Nasal Decongestants.)

C. Principles Applicable to Combination Products

1. General combination policy. Most cold, cough, allergy, bronchodilator and anticholinergic products currently in the marketplace containing more than one active ingredient are marketed as combination products. These combinations of ingredients must be adequate for the treatment of the symptom or symptoms which the combination product is intended to control. The Panel feels that the proper use of combination products can be rationalized if adequate directions for use and warnings against the use of a combination product unless each of the combination product contains only active ingredients contributed to the claimed effects and that each active ingredient must be necessary for rational therapy of concurrent symptoms. The Panel is familiar with the arguments for combination products and at the same time recognizes the disadvantages of combination products. One major disadvantage commonly expounded is the inability to permit individualized dosage of each active ingredient. The Panel agrees in principle that the combination product contains only active ingredients at doses of demonstrated safety and effectiveness and all ingredients which are necessary for treatment of symptoms, the Panel concludes that certain combinations may offer a convenient and rational approach for relief of concurrent symptoms.

The Panel refers to a recognized source of drug information which notes that cold remedy mixtures are widely used and enjoy a certain amount of acceptance by the medical profession and the laity. It is the view of the Panel that certain combinations, as established by the Panel are acceptable and summarized below. (See part II, paragraph 4.) To support this view, the Panel refers to the conclusion in the above-referred text (Ref. 1) which states—"a physician may prescribe a remedy must be certain that the ingredient preparation containing only an antihistamine should not be used alone for the relief of symptoms because of the current OTC market scarcity of single drug preparations.

In fact, of the 339 volumes received as submissions for review by the Panel, only 44 volumes contained data concerning 24 single active ingredients being marketed in OTC products. This represents 24 single active ingredients, out of a total of 153 active ingredients submitted by firms, as being present in marketed OTC CCABA products. The 46 products containing the single active ingredients represented a wide variety of dosage forms which included aerosols, liquids, tablets, syrups, drops, sprays, jellies and elixirs. The Panel has prepared the following table of the 24 single active ingredients marketed in CCABA products and submitted to the Panel for review:

PROPOSED RULES

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
The Panel concludes that in light of the numerous CCABA combination products on the market, there appears to be a shortage of single active ingredient products for the consumer to adequately and individually treat a specific symptom. This may or may not be representative of the marketplace but certainly indicates a paucity of single ingredient products.

The Panel is aware of the inclusion of inactive, i.e., nontherapeutic, ingredients from pharmacologic groups. Therefore, the concept that it may be more convenient to include more than one active ingredient in the same product. The concept of the "common cold" or hay fever may include nasal congestion, running nose and coughing. The Panel has determined that if a combination product takes contains ingredients which are limited to one active ingredient from each representative pharmacologic group, e.g., nasal decongestant, antihistamine and antiinflammatory each of which is generally recognized as safe and effective when used alone for the specific symptom, e.g., antiinflammatory for cough, the combination is rational and convenient for treatment of concurrent symptoms. The Panel concludes that the combinations of ingredients from pharmacologic groups identified below are safe and effective for a significant population having concurrent symptoms. (See part II paragraph G.8.b. below—Criterion.)

The Panel clearly desires to avoid the so-called "shotgun approach" for the treatment of symptoms with a combination of ingredients in a single product. However, due to the unique nature of symptoms to be treated by CCABA preparations under consideration by this Panel, such combinations, with restrictions as established by the Panel, are justifiable.

The Panel is aware of a regulation (21 CFR 331.15(b)) providing for the combining of safe and effective (Category I) ingredients with different pharmacologic activities. This concept has been adopted by this Panel for certain combinations that the Panel has classified as Category I. The Panel believes that these combinations of pharmacologic groups identified as Category I may offer a convenient and rational approach for relief of concurrent symptoms. The Panel has limited such combinations to three pharmacologic groups because it is unlikely that concurrent symptoms of sufficient duration and severity exist to warrant such combinations. As previously noted, drugs in the same category pertaining to the "common cold," the course and symptoms of the disease are variable and may extend for 7 to 14 days. It would appear highly unlikely that at any one time, simultaneous symptoms would be present of sufficient intensity in the course of the disease as to warrant the need for a product containing more than three pharmacologic groups. Therefore, the Panel has determined that combination products containing four or more different pharmacologic groups be classified as Category III. Before such products may be considered as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified.

A. Combinations of active ingredients reviewed by the Panel from the same pharmacologic group. The Panel is concerned with the marketing of products containing drugs from the same pharmacologic group. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group. The Panel can find little scientific justification for combining more than one active ingredient from the same pharmacologic group in the same product. The Panel is unaware of adequate supportive data which would establish sufficient argument for combining ingredients from the same pharmacologic group. For most products reviewed by the Panel, these ingredients from the same pharmacologic group are present in subtherapeutic doses. There is a lack of data on the effects of full therapeutic doses of ingredients from the same pharmacologic group in combination and therefore such combinations could not be evaluated by the Panel.
The Panel has reviewed, for example, anti-claims do not directly relate to the active containing these ingredients. Such to headache, aches, pains and fever due of nine sulfate and salicylamide. Claims These ingredients include acetaminophen, being reviewed by Category III combinations of ingredients from the same pharmacologic group. It is the opinion of the Panel that to provide for combinations containing ingred-
iments from the same pharmacologic group would contribute to the likelihood of undesirable additive or synergistic ef-fects as noted above. (See part II, para-graph C.2. above—Limitation of ingredient in combination products.) It is ac-
cepted medical practice to give only those drugs necessary for the safe and effec-tive treatment of the patient. The Panel believes that this concept should also apply to self-medication where a con-summer treats symptoms without the ad-vise of a physician.

In conclusion, to allow for the possi-bility, however unlikely, that there may be advantages to combining two drugs from the same pharmacologic group, the Panel has determined that such combina-tion(s) be classified as Category III. Additional studies as described below in Principle 10 are needed for Category III combinations to determine their safety and effectiveness. (See part II, paragraph 10. below—Criteria and testing procedures for Category III combi-nation products (for oral use unless other-wise specified).) The Panel has further determined that any combination prod-uct containing more than two active ingred-
iments from the same pharmacologic group (e.g., three antihistamines) is ir-rational since there seems to be no rea-
son to expect a possible benefit from the combination, one drug therefore classified by this Panel as a Category II combination.

5. Combining of active ingredients not reviewed by the Panel from the same or different pharmacologic group. Many CCABA preparations contain active ingred-
iments that have not been reviewed by this Panel because they are ingred-
iments that have been or currently are being reviewed by other OTC panels. These ingredients include ascorbic acid, aspirin, benzocaine, caffeine, quinone sulfate and salicylamide. Claims such as “for temporary relief of headache, aches, pains and fever due to colds” are examples of the labeling commonly found on CCABA preparations containing these ingredients. Such claims do not directly relate to the active ingredients reviewed by this Panel. The Panel has reviewed, for example, ant-


- antihistamine containing CCABA preparations with labeling claims for the prevention or treatment of the common cold. The Panel has reviewed the available data for the ingredient as a single entity and finds that the data are insufficient to permit final classifica-
tion as to the safety and effective-ness of individual antihistamines, for ex-
ample, remains with the OTC Internal Analgesic Panel. The following are the Panel’s conclusions as to the appropri-
ateness of such combinations:

a. Combination products containing vitamins. The Panel is cognizant of the popular use of vitamin C (ascorbic acid) for the prevention or treatment of the common cold. The Panel has reviewed the available data for the ingredient as a single entity and finds that the data are insufficient to permit final classifica-
tion as to the safety and effective-ness of OTC use in the prevention or treatment of the cold. The Panel has discussed the safety and effectiveness of vitamins including vitamin C as claimed active ingredients elsewhere in this document. (See part IX, paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the common cold.) and (See part IX, paragraph B.3.b. below—Ascorbic acid (vitamin C). The Panel has also discussed the labeling of these claimed active ingre-dients elsewhere in this document. (See part IX, paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the common cold.) and (See part IX, paragraph B.2.b. below—Ascorbic acid (vitamin C).)

The Panel found no study which demon-
strated that vitamin C is unequivocal-
ly effective for the prevention or treat-
ment of the common cold although such data tended to favor ef-fectiveness for treatment of cold symp-
toms. Since no conclusive data on the dose or dosage schedule are available on the safety of combination products with other ingredients for pre-
vention or treatment of the cold, the Panel is unable to propose adequate labeling for a dosage regimen and has therefore classified vitamin C as Category II. In summary, the Panel has reviewed vitamin C and has classified the “ingredient” as Category III and any labeling claims for use in the prevention or treatment of the cold as Category II.

With regard to combination products, the Panel further notes that the use of vitamins in a CCABA combination product containing an antihistamine with sleep-aid claims to be acceptable and rational. Therefore, where not expressly prohibited, a generally recognized as safe and effective antihistamine or other agent may be combined with the Category I ingredients reviewed by the Panel. Certain combinations that are contradi-
cated and placed in Category II are summarized below. (See part II, paragraph C.9.b. below—Criteria for Category II combi-
novation products containing local anesthetics or other agents with

“common cold” in combination products which are to be used only for a short time, and would be illogical for a consumer to take a cold combination product to prevent a cold. The Panel has therefore placed the labeling claims of combination prod-

- cements containing antihistamines with sleep-aid claims. Antihistamines are primarily useful for relief of allergic disorders but secondarily act centrally to produce sedation or sleep. The Panel has discussed the safety and effectiveness of antihistamines elsewhere in this document. (See part VII, below—Antihistamines.) The Panel has established a safe and effective dosage range for certain antihistamines when used to treat symptoms of running nose, sneez-
ing, itching nose or throat and watery eyes. The Panel has recommended that the labeling for these ingredients con-
tain the warning, “May cause drowsi-
ness”.

The Panel notes that CCABA combi-
nation products are currently available in a single-entity and a combination form. The Panel recognizes that if the symptoms of cold and cold are adequately treated, there is a greater likelihood of normal sleep. However, the duration of drug ef-

- fects from “nighttime cold preparations” which are recommended to be taken once at bedtime is not fully documented.

The Panel is unable to make a final determination as to safe and effective use of an antihistamine or other agent when used as a sleep-aid in CCABA prepara-
tions. It is obvious an antihistamine may have several activities, e.g., antihistamine, antiallergic, antitussive, antipyretic, or sedative activity de-pending upon the dosage level used. The Panel has therefore placed sedation claims associated with CCABA combina-
tion products containing an antihista-
mine in Category III. The Panel further concludes that the combining of an addi-
tional antihistamine in a CCABA combi-
nation product for some dosage form of sedation is irrational. Therefore, the Panel classifies such combinations as Category II.

d. Combination products containing local anesthetics or other agents with

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nation product for some dosage form of sedation is irrational. Therefore, the Panel classifies such combinations as Category II.

d. Combination products containing local anesthetics or other agents with
claims for relief of sore throat. The symptoms of sore throat often accompany upper respiratory infections, which are usually a simple irritation aggravated by breathing through the mouth. The Panel has referred the evaluation of the safety and effectiveness of active ingredients and labeling claims for sore throat to the OTC Oral Cavity Panel. The Panel believes that combination products containing safe and effective agents to relieve minor throat irritation are rational. The Panel has therefore placed combinations containing local anesthetics with other Category I CCABA-agents in Category I. The Panel recommends that labeling contain adequate warnings against use when persistent or chronic sore throat is present and is accompanied by fever or other symptoms. (See part F. paragraph F. below—Deferral of “Sore Throat” Claim.)

The Panel recognizes that most sore throat remedies are applied topically while other symptoms of the cold are usually treated internally through oral ingestion. As an example, a throat lozenge containing a local anesthetic (benzocaine) and dextromethorphan produces two pharmacologic activities. The lozenge releases benzocaine locally in the oral cavity whereas the dextromethorphan is ingested for its sedating side effects of antihistamines.

e. Combination products containing correctives (stimulants and sedatives).

The Panel is aware that caffeine is included in some CCABA preparations with claims such as “for relief without drowsiness.” Caffeine is also sometimes added to a combination product with no reference in the labeling as to its pharmacologic activity. The Panel presumes that the rationale for the inclusion of caffeine in such combinations is to reduce the sedating side effects of antihistamines.

While the Panel agrees with the rationale for caffeine serving as a “stimulant corrective,” combinations containing it are placed in Category III until such time as a “corrective” pharmacologic activity of caffeine can be proven. This activity of caffeine should be identified on the label as “an ingredient added to counteract drowsiness caused by the product.” Where caffeine is added only as a corrective, labeling claims such as “for relief without drowsiness” are unjustified and are therefore misleading. The Panel has classified such labeling claims as Category II.

The Panel believes that combining Category I CCABA ingredients with a stimulant such as caffeine at a fully effective dose (not as a corrective) is irrational since the Panel is unaware of a significant target population having a need for both antihistaminic and a stimulant. Accordingly, the Panel places combinations of CCABA ingredients combined with stimulants at effective dosage levels in Category II.

In addition, adding sympathomimetic drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this effect the Panel presumes that phenobarbital has been added to some combinations as a “sedative corrective” rather than as an active ingredient. While the Panel agrees with the need for additional medicinal substances, it prefers such substances serving as a “sedative corrective,” combinations containing it are placed in Category III until such “corrective” pharmacologic activity of the product can be proven. (See part IX, paragraph B.2.d. below—Phenobarbital.) This activity of phenobarbital should be identified on the label as “an ingredient added to counteract nervousness caused by the product.” The Panel has included in this document a protocol designed to evaluate the effectiveness of phenobarbital under the above circumstances to show whether it has an additional beneficial or adverse effect on bronchospasm. (See part IX, paragraph B.2.d.(5) below—Evaluation.)

f. Labeling of active ingredients. As discussed above, the Panel has determined that each claimed active ingredient in a combination product must make a contribution to the claimed effect(s). (See part II, paragraph C.1. above—General combination policy.) Based upon this determination, the Panel concludes that “combination products must be labeled to reflect the therapeutic capabilities of each active ingredient in the combination. If a single ingredient has several activities, these should all be labeled consistent with the activities found at the recommended dosage for the product.

The Panel recommends that the labeling of a combination product containing active ingredients for treatment of concurrent symptoms emphasize the use of the product only when all such symptoms are present. The consumer should be adequately informed through the labeling of the therapeutic capabilities of the product. If, for example, only the symptom of running nose is present, a single ingredient rather than a combination product would be the rational therapy. Labeling should therefore fully reflect the activities of all active ingredients at the dosage recommended so that a combination product is not labeled for relief of concurrent symptoms. If a product contains an active ingredient for which no labeling claim is made, it is clearly misleading to the consumer.

7. Marketing experience for cold, cough, allergy, bronchodilator and antihistamine combination products.

The Panel recognizes the extensive marketing history of CCABA preparations. The drug industry presented data to the Panel summarizing consumer complaint information obtained from a survey of 32 pharmaceutical manufacturers. (See part I. paragraph 9.) A total of 117 combination CCABA products representing over 4 billion package units were included in the survey. The survey products were combinations of 83 ingredients representing 9 pharmacologic groups (nasal decongestants, antitussives, expectorants, antihistamines, antiinflammatory drugs, bronchodilators, medications for cold, allergy, and antihistamines). The survey included active ingredients such as glycerin and alcohol which were also included in the data presented.

The drug industry reported to the Panel that the overall number of consumer complaints in the survey, in terms of either adverse reactions and/or ineffectiveness was less than one complaint per million packages sold. However, from the survey data the Panel is unable to determine whether the information on adverse reactions was gathered during the period for which marketing data were reported for the products. The drug industry acknowledged that not every consumer complaint is well-founded or attributable to the drug product. The Panel believes that a single product fails to receive relief or experiences side effects registers complaints with the drug manufacturer.

The Panel has considered the marketing data submitted. The Panel finds that of the 83 ingredients included in the survey, only 11 ingredients have been classified by the Panel as Category I whereas 27 have been classified as Category III. Only one of the ingredients, belladonna alkaloids, has been classified as Category II when used by inhalation in the treatment of asthma. The remaining ingredients were not submitted for review to the Panel, pursuant to the call for data published in the Federal Register of August 9, 1972 (37 FR 16032), and therefore have not been evaluated by the Panel. Several of these ingredients are currently available only by prescription while others are inactive ingredients. The Panel does not consider active ingredients contained in the products and the amounts actually consumed by consumers were not included in the survey data and can only be estimated. It would appear from the data that there is a low incidence of obvious adverse reactions which the consumer can attribute to the drug product. Since the quantities of drug administered in the surveyed products are not known, the Panel has reviewed the quantities of active ingredients contained in the marketed products submitted for review to the Panel. (See part I. paragraph 1. above—Submissions by Firms.) The Panel presumes that the quantities of active ingredients contained in these products are generally representative of the products contained in the survey. The Panel concludes that while marketing data are limited and difficult to interpret they tend to support the safe use of combinations of active ingredients reviewed by the Panel.

The fact that over 4 billion packages of the 117 combination products have been sold tends to indicate that consumers perceive a need for combination products. It is obvious that consumers believe these products useful, to account for the many sales, but the extent to which this belief by the consumer is established by advertising rather than by a need perceived independently of advertising cannot be determined by the Panel. In addition, the benefits of a product may be related to a placebo response and also to the fact that a self-limiting illness is being treated.

Regarding ineffectiveness, the Panel has applied the OTC Drug Data Base (21 CFR 330.10(a) (4) (d)II) which provides, that as a source of corroboration for proof of effectiveness, the reports of significant human experience during
8. **Criteria for Category I combination products (for oral use unless otherwise specified).** Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. **Criterion.** Each claimed active ingredient and its labeling in a combination must be generally recognized as safe and effective (Category I) and such ingredients are present in amounts within the effective dosage range.

b. **Criterion.** Products containing one active ingredient from each pharmacologic group in the combinations identified below are classified as Category I combination products, provided the active ingredients and their labeling are generally recognized as safe and effective (Category I) and such ingredients are present in amounts within the effective dosage range.

(1) Combinations containing an analgesic-antipyretic and an antihistamine.

(2) Combinations containing an analgesic-antipyretic and a nasal decongestant.

(3) Combinations containing an analgesic-antipyretic, a nasal decongestant and an antihistamine.

(4) Combinations containing an antihistamine and an antitussive provided the product is labeled only for nonproductive cough. "Caution. If a product contains an active ingredient or labeling that has not been reviewed by this or other OTC Advisory Review Panels, such ingredient or labeling is classified as Category II if it includes any ingredient(s) at less than the minimum effective dosage established by the Panel unless the labeling states that the product is for use only to treat the same symptom."

(5) Combinations containing an antihistamine and a nasal decongestant.

(6) Combinations containing an antihistamine, an antitussive and a nasal decongestant.

(7) Combinations containing an antihistamine, an antitussive and an expectorant provided the product is labeled only for nonproductive cough. Expectorants are expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions. Antitussives suppress the act of coughing and may promote retention of some mucous secretions and thereby coat inflamed bronchial membrane linings.

(8) Combinations containing an antitussive and a nasal decongestant.

(9) Combinations containing an antitussive and a local anesthetic or local analgesic-anti-pyretic provided the product is labeled only for cough. Local anesthetics may produce thickened bronchial secretions whereas the anticholinergic bronchodilator and an antitussive when the product is labeled only for cough associated with asthma. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic bronchodilator produces an opposite effect, i.e., anti-secretory action.

(10) Combinations containing a bronchodilator and an antitussive.

(11) Combinations containing a nasal decongestant and a local anesthetic or local analgesic-anti-pyretic provided the product is available only as a lozenge.

(12) Combinations containing an oral bronchodilator (sympathomimetic) and an oral bronchodilator (theophylline).

(13) Combinations containing an antihistamine and an expectorant and a nasal decongestant.

(14) Combinations containing an antihistamine and an antitussive when the product is labeled only for cough associated with asthma. This combination is irrational because the antihistamine suppresses cough and the cough is essential in asthma to maintain an open airway by clearing the respiratory passages of excessive secretions.

9. **Criteria for Category II combination products (for oral use unless otherwise specified).** Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. **Criterion.** A combination is classified as Category II if it includes any ingredient(s) at less than the minimum effective dosage established by the Panel unless the labeling states that the product is for use only to treat the same symptom. (See Part II, paragraph C. 10.b.(1) below—Category III Combination.)

b. **Criterion.** A combination product containing Category I ingredients from different pharmacologic groups is classified as Category II if it includes any ingredient(s) at less than the minimum effective dosage established by the Panel unless the labeling states that the product is for use only to treat the same symptom. (See Part II, paragraph C. 10.b.(1) below—Category III Combination.)

c. **Criterion.** If a product contains an active ingredient or labeling that has not been reviewed by this or other OTC Advisory Review Panels, such ingredient or labeling is classified as Category II if it includes more than two active ingredients from the same pharmacologic group.

d. **Criterion.** A combination product is classified as Category II if it includes any ingredient(s) at less than the minimum effective dosage established by the Panel unless the labeling states that the product is for use only to treat the same symptom. (See Part II, paragraph C. 10.b.(1) below—Category III Combination.)

e. **Criterion.** A combination product containing active ingredients and labeling which have been determined by the Panel to be unsafe or irrational and classified as Category II is not safe because of concurrent symptoms where an asthmatic needs relief of asthma, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(2) Combinations containing an antihistamine and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic bronchodilator produces an opposite effect, i.e., anti-secretory action.

(3) Combinations containing an antihistamine and a local anesthetic or local analgesic-anti-pyretic provided the product is labeled only for cough. Local anesthetics may produce thickened bronchial secretions whereas the anticholinergic bronchodilator produces an opposite effect, i.e., anti-secretory action.

(4) Combinations containing an oral bronchodilator and an antihistamine. This combination is irrational because the anticholinergic bronchodilator may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(5) Combinations containing a bronchodilator and an antihistamine. This combination is irrational because the anticholinergic bronchodilator may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(6) Combinations containing an antihistamine and an anti-cholinergic and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic bronchodilator may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(7) Combinations containing an antihistamine and an anti-cholinergic. This combination is irrational because the anticholinergic bronchodilator may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(8) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antihistamine. This combination is irrational because the antihistamine and the antitussive are claimed for the same cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of the antihistamine to control symptoms contained in the preparation. In addition, the Panel concludes that a bronchodilator should only be labeled for use in individuals with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or anti-pyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(9) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistamine and the antitussive are claimed for the same cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of the antihistamine to control symptoms contained in the preparation. In addition, the Panel concludes that a bronchodilator should only be labeled for use in individuals with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or anti-pyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(10) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistamine and the antitussive are claimed for the same cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of the antihistamine to control symptoms contained in the preparation. In addition, the Panel concludes that a bronchodilator should only be labeled for use in individuals with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or anti-pyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(11) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistamine and the antitussive are claimed for the same cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of the antihistamine to control symptoms contained in the preparation. In addition, the Panel concludes that a bronchodilator should only be labeled for use in individuals with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or anti-pyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(12) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistamine and the antitussive are claimed for the same cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of the antihistamine to control symptoms contained in the preparation. In addition, the Panel concludes that a bronchodilator should only be labeled for use in individuals with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or anti-pyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

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(14) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistamine and the antitussive are claimed for the same cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of the antihistamine to control symptoms contained in the preparation. In addition, the Panel concludes that a bronchodilator should only be labeled for use in individuals with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or anti-pyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.
suggest the product for the prevention or treatment of the "common cold." (See part II, paragraph C.5.a., above.) Combination products containing stimulants and sedatives should be evaluated by the minimum effective dosage established elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of Category I ingredients from different pharmacologic groups used to treat the same symptom and in which at least one of the ingredients is in less than the minimum effective dosage, to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects should not be significantly greater than those of any individual ingredient in that combination alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than any one of the ingredients when tested alone in the minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose a greater risk of side effects than is associated with an ingredient alone in its minimum effective dosage.

c. Criterion. (1) Category III combination. A combination product is classified as Category III if it includes two Category I ingredients from the same pharmacologic group.

(2) Category III testing procedure. An acceptable test procedure will be one in which the combination, each of the individual ingredients alone, and a placebo are evaluated, all in the same study, against the relevant symptom (labeling claim). In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual ingredients and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than either ingredient when tested alone in its minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose greater risk of side effects than is associated with an individual ingredient alone in the minimum effective dosage.

c. Criterion. (1) Category III combination. A combination product containing two Category I ingredients from the same pharmacologic group is classified as Category III if it includes either or both ingredients at less than the minimum effective dosage established by the Panel.

(2) Category III testing procedure. An acceptable test procedure will be one in which the combination, each of the individual ingredients in the minimum effective dosage, and each of the individual ingredients in the less than the minimum effective dosage used in the combination, and a placebo are evaluated, all in the same study, against the relevant symptom. In this way, comparisons of safety and effectiveness can be made directly between the effects of the individual active ingredients from the same pharmacologic group and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than either individual ingredient when tested alone in its minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose a greater risk of side effects than is associated with an individual ingredient alone in the minimum effective dosage.
determination and are classified as Category III: (i) Combinations containing atropine and an oral nasal decongestant. Additional studies are necessary to assess the potential additive central nervous system stimulant side effects.

(ii) Combinations containing an antihistamine and an oral nasal decongestant. Additional studies are necessary to assess the nature and extent of additive anticholinergic side effects.

(iii) Category III testing procedure. An acceptable test procedure will be one in which the combination and a placebo are evaluated in suitable subjects so that comparisons can be made of the particular side effect(s) of concern which are specified above. In addition, data on the relative incidence and intensity of these side effects must be available for the individual active ingredients in the same dosage as in the combination either evaluated in the same study as above or evaluated in a separate study using a comparable test protocol. The appropriate protocol(s) under the heading “Data Required for Evaluation” are identified elsewhere in this document for each respective pharmacologic group.

If the relative incidence and intensity of the side effect(s) of the combination are increased to a degree which precludes its safe use as an OTC product, it will be classified as a Category II combination for those dosages. If the relative incidence and intensity of side effect(s) are significantly greater than either ingredient administered alone but not to a degree to prevent its safe OTC use, a suitable warning regarding potential for that side effect should be specified in the labeling for the combination product. If the relative incidence and/or intensity of side effect(s) with the combination are not significantly greater than with either ingredient administered alone, no warnings other than the standard Category I warnings for those ingredients are needed on the label.

(d) Criterion. (1) Category III combinations. Combinations of active ingredients for which the available effectiveness data are insufficient for the Panel to make a final determination or for which there is no rationale for use as classified as Category III are as follows: (i) Combinations containing a nasal decongestant and an antihistamine administered topically as a spray or drops. Additional studies are necessary to assess the contribution of the antihistamine administered by the topical route since there are inadequate studies demonstrating the effectiveness of the antihistamines topically in such combinations.

(ii) Combination products containing an antihistamine and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an antihistamine in reducing cough.

(iii) Combination products containing an antihistamine and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an antihistamine in reducing cough.

(iv) Combination products containing an antihistamine and an expectorant provided the product is labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antihistamine and an expectorant in the presence of excessive or more fluid bronchial secretions.

(v) Combination products containing an antihistamine, an expectorant and a nasal decongestant provided the antihistamine and expectorant ingredients in the product are labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antihistamine and an expectorant in the presence of excessive or more fluid bronchial secretions.

(b) Category III testing procedure. An acceptable test procedure will be one in which the combination, each of the individual ingredients in the dosage used in the combination, and a placebo must be evaluated against the relevant symptom (labeling claim), either in the same study, or in separate studies using comparable test protocols. The appropriate protocol(s) under the heading “Data Required for Evaluation” are identified elsewhere in this document for each respective pharmacologic group. When tested alone, each individual ingredient should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a “contribution.” Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For the combination of Category I ingredients from different pharmacologic groups to be a Category I combination by that route of administration, the combination must also exert a significant effect against each of the relevant symptoms when compared to the placebo.

For the combination of Category I ingredients from different pharmacologic groups to be a Category I combination by that route of administration, the combination must also exert a significant effect against each of the relevant symptoms when compared to the placebo.

(c) Category III testing procedure. An acceptable test procedure will be one in which the combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence and/or intensity of the undesirable side effect, and to assess the safety of this combination.

(d) Criterion. (1) Category III combinations. There is lack of data on a suitable placebo for use in the treatment of concurrent symptoms of sufficient duration to justify combination products containing four or more different pharmacologic groups. Therefore, the Panel classifies combination products containing four or more different pharmacologic groups as Category III. Examples of such combinations are as follows: (1) Combinations containing an analgesic-antipyretic, an antihistamine, an expectorant and a nasal decongestant.

(2) Combinations containing an analgesic-antipyretic, an antihistamine and a nasal decongestant.

(3) Combinations containing an analgesic-antipyretic, an antihistamine and a sleep-aid drug.

(e) Category III testing procedure. Before such combinations may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified for appropriate epidemiologic studies. If a suitable target population is...
found such combinations may be classified as Category I.

REFERENCES
(2) OTC Volume 402025.

D. STATEMENT ON CATEGORY III TESTING PROCEDURES

I. Comments on study design. The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances in or improved techniques for such studies.

Experimental design should take into account the need to include a sufficient number of subjects or trials so as to provide meaningful conclusions which can be supported by statistical analysis. The selection of appropriate subjects or patients can be of major importance when the effect of a drug in a specific illness or symptom is under study.

A role for bias is assumed in all situations wherein the subject, the observer or both make a judgment as to the nature of magnitude of a response. Biases also contribute to variation in response between individuals in a given study sample. Although biases and biological variation cannot be eliminated, their effect on the outcome of an experiment can be avoided or minimized by adopting a "double-blind, placebo-controlled" or other suitably blinded design. In such a design, one group of subjects receives a placebo or dummy preparation so that the response unmodified by drug under test can be established. Neither the subjects nor the observer should be able to detect the identity of the preparations under test. This requires that the test and placebo preparations be indistinguishable in regard to taste, color and shape except in the case of preparations containing volatile substances where it will be impossible to make the active ingredients indistinguishable from the placebo.

It is often desirable to include a standard drug (a drug used as a positive control known to exert a significant effect against the relevant symptom(s) being tested) with which the unknown can be compared. Finally the inclusion of two or more doses of the drug under test may be desirable in order to provide an estimate of an effective therapeutic dose range free from undesirable side effects.

If a crossover design is utilized, i.e. each subject serves as his own control, the sequence in which the placebo, standard and test drugs are administered should be randomized and a sufficient "washout period" between tests should be permitted.

Wherever possible, objective measurements should be made in preference to subjective judgments. However, such measurements may not be applicable to the symptom or symptom complex for which the drug under test is to be used.

2. Testing period provided for Category III combination products concludes that the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective, or would result in misbranding to remain in use for the period of time specified below after the date of publication of the final monograph in the Federal Register, if the manufacturer or any such combination product utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to such condition by the Panel. The Panel has established the following specific time limitations for testing based upon the applicable pharmacological group:

- **Pharmacologic group:**
  - Anticholinergic: 3 years
  - Antihistaminic: 3 years
  - Antitussive: 4 years
  - Bronchodilator sympathomimetic: 3 years
  - Bronchodilator sympathomimetic: 3 years
  - Expectorant: 5 years
  - Nasal decongestant: 6 years

The Panel believes that testing for bronchodilators, antihistamines, anticholinergics and nasal decongestants can be completed within the techniques for testing are all well-established and are discussed in the relevant sections of the document below. The Panel feels that 1 year is necessary for the development of techniques and data provided for the actual testing. Clinical testing should start within 6 months of publication of the final monograph.

The Panel recognizes that caffeine serving as a "stimulant corrective" elsewhere in this document (See part II paragraph C-5.6., above) and other combinations containing antihistamines with sleep-aid claims.

The Panel is aware of the inclusion of caffeine in some CCABA preparations with claims such as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II paragraph C-5.6., above). Combination products containing antihistamines with sleep-aid claims.

The Panel recognizes that CCABA combination products are available for use at bedtime and promoted for such various claims as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II paragraph C-5.6., above). Combination products containing antihistamines with sleep-aid claims.

The Panel has therefore placed sedation claims associated with CCABA combination products containing antihistamines in Category III and has provided 3 years for testing and documentation of such claims.

Time provided for testing (years)

- **Category III conditions:**
  - Antihistamines with sleep-aid claims: 3 years
  - Caffeine (stimulant corrective): 2 years
  - Phenobarbital (sedative corrective): 2 years
  - Timed-release drug formulations: 4 years
  - VAZ (gaseous acid): 1 year

The Panel recognizes that CCABA combination products are available for use at bedtime and promoted for such various claims as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II paragraph C-5.6., above). Combination products containing antihistamines with sleep-aid claims.

The Panel recognizes that CCABA combination products are available for use at bedtime and promoted for such various claims as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II paragraph C-5.6., above). Combination products containing antihistamines with sleep-aid claims.

The Panel recognizes that CCABA combination products are available for use at bedtime and promoted for such various claims as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II paragraph C-5.6., above). Combination products containing antihistamines with sleep-aid claims.
PROPOSED RULES

EFFECT OF TIMED-RELEASE FORMULATIONS ON EFFECTIVENESS AND SAFETY OF OTC DRUG PRODUCTS

1. Introduction. The oral route is the most common method of administration for OTC cold, cough, allergy, bronchodilator, and antihistaminic products. Such products are swallowed and absorbed from the stomach and intestines. Drugs administered orally or by inhalation in gastrointestinal fluids and are absorbed into the systemic circulation where they exert an action on "target" organs or receptors. Generally, this action occurs within an hour or so of ingestion of the drug and peaks, e.g., in an hour or two, but the drug action lasts for several hours, e.g., 3 to 6 hours. When the drug action begins to decline, e.g., at the end of 3 to 6 hours, it is necessary to take another dose so that the desired action will continue at a more or less constant level. Most drug studies showing safety and effectiveness of drugs rely upon oral dosage forms that act in this manner. There are, however, a number of OTC CCABA products that are formulated in another kind of oral dosage form called timed-release formulations. Theoretically, these products are formulated so as to dissolve in gastrointestinal fluids in a controlled manner so that small amounts will be absorbed over a longer period of time, e.g., 3 to 6 hours rather than 1 hour, and the duration of drug action will be extended over a long period, e.g., 8 to 12 hours rather than 3 to 6 hours.

Since the specific formulation of a product can affect its safety and effectiveness, the Panel has considered timed-release formulations of these products under its review. The Panel did not consider in detail each of these formulations nor evaluate the dissolution times of the specific formulation or the effect of formulation on the rate of release of each individual ingredient under review when formulated in this unique manner. The Panel does recognize certain advantages of timed-release formulations. The Panel has reviewed the pertinent literature and selected articles regarding timed-release formulations and has set forth certain guidelines to be used in their evaluation (Refs. 1 through 9).

2. General discussion. To produce its characteristic effect, a drug must achieve adequate concentrations at its site of action. One important factor in determining the concentration attained is the extent and rate of drug absorption. Other factors include the amount of drug administered and the body's ability to maintain the drug at effective levels, the body's metabolism and excretion.

The latent period between administration of a drug and its onset of action is influenced by the route of administration, e.g., orally, topically, by inhalation, etc., and the rate of absorption and the penetration of the drug to the site of action. The duration of drug effects is determined largely by the rate of inactivation and excretion of the drug. The duration of action of the drug effect is dependent on several factors.

The rate of absorption of oral dosage forms is dependent largely on their dissolution rate in gastrointestinal fluids. Theoretically, slow release and sustained effects (up to 8 or more hours) of drugs administered in oral dosage forms should be attained if such drugs are formulated so as to dissolve in gastrointestinal fluids in a controlled manner.

A number of the active ingredients reviewed by the Panel are presently formulated in repeat action or extended release dosage forms. These formulations are known by a variety of names such as sustained action, sustained release, prolonged release, controlled release, long-acting time release, etc. Repeat-action tablets periodically release complete doses of active drug to the gastrointestinal fluids. Extended-release tablets contain ingredients that prolong the contained medication to the gastrointestinal fluids. These terms are often used interchangeably and, although technically different, are referred to in this document as timed-release formulations.

3. Advantages. The principle of controlled release of drugs from oral dosage units is generally accepted to provide several advantages over the conventional dosage forms that require a shorter time interval regimen of administration.

Among these advantages may be listed the principal ones of better patient compliance, increased patient convenience, and lower incidence and/or severity of side effects of the drugs due to elimination of the peaks in the level of drug concentration in the blood that often occur following administration of traditional dosage forms.

4. Disadvantages. Among the disadvantages is the fact that uniformly effective preparations of time-released drugs have been difficult to produce because of technical problems associated with their manufacture, but also because the dissolution rate of these preparations in the body may be irregular, and because variations in gastrointestinal acidity, gastric emptying, and intestinal motility and other physiological factors also influence drug absorption.

If responsible uniformity of effectiveness is not achieved, for whatever reason, the dissolution rate, for example, may be so slow that no effect is achieved or, conversely, it may be so fast that the patient receives the effect of all the active drug within a short time period, resulting in an increased incidence and/or severity of side effects.

In some instances, there are a number of reasons why a given drug should not be formulated as a timed-release product. These reasons relate to the inherent nature of a specific drug. For example, a drug may have a very long half-life, i.e., it may be metabolized and eliminated from the body over a long period of time, and thus conventional dosing already provides sustained blood levels. A drug may require a very large dose before sustained action is possible and a timed-release product containing a dose sufficient for 8 or 12 hours would necessitate an inconvenient amount of drug being swallowed. Potent drugs, i.e., those having a very small difference between the effective and toxic doses, or those to which patient response is variable, necessitate individualization of dose or dosage interval, and timed-release products are designed to release the drug in a fixed pattern. Drugs that are poorly or incompletely absorbed or metabolized may not be absorbed erratically, and thus the predictability of response following ingestion of a timed-released product is difficult. Since the amount of drug contained in a timed-release formulation is usually greater than in a conventional formulation, increased side effects or toxicity is possible. Variations in the patient's physiological response or a technical flaw in the formulation may result in the release of more than the entire amount of active drug from the formulation in a short period of time, thus producing a toxic level.

Some drugs reviewed by the Panel are inappropriate for formulation in a timed-release product. Glyceryl guaiacolate is a drug that for effectiveness requires a relatively large dose at regular intervals. Thus, the dose of the drug required to obtain an effective action over an extended period of time, e.g., 8 to 12 hours, would be difficult to swallow. The theophylline represents an example of a potent drug for which patient dosage should be individualized because of the drugs' variable rates of metabolism. Such drugs as salicylates have a variable action depending upon the rate of absorption.
individualization of dosage is best obtained by ingestion of small doses of theophylline formulations than are possible with timed-release products.

All other drugs reviewed by the Panel would, on theoretical grounds, be suitable for inclusion into a timed-release product. For approval of any drug in a given type of timed-release formulation, evidence should be presented to demonstrate that blood levels and areas under blood drug-level curves, which can be predicted in evaluation of time-release formulations because the area under the blood drug-level curve of such a formulation should approximate that obtained with appropriately repeated doses of a conventional oral form of the drug. Thus, for example, two experimental approaches may be considered: For core formulations, the urine excretion measurements offer an alternative approach. Where appropriate, it is preferable to measure blood levels of the parent drug and/or its metabolites; however, urinary excretion measurements offer an alternative approach.

5. Guidelines for evaluation of timed-release formulations. Timed-release formulations generally fall into one of three major categories: Extended release—those that provide for gradual and continuous release of active substance along the gastrointestinal tract; repeated action—those that provide two or more essentially discrete release times for the active constituents, e.g., coat/core formulations; and those that combine the mechanisms of both of the foregoing kinds of formulations.

Evaluation of any type of long-acting oral formulation should accomplish two objectives. First, it should establish that the dosage form provides delayed absorption of the drug and/or when the metabolism of the drug is well understood. In utilizing measurements of urinary levels and excretion rates, the timed-release product should also be compared with suitably repeated doses of a conventional oral form of the drug. With both preparations, the urinary excretion levels and rates over the test period should be roughly similar but need not exactly match.

6. Summary. This concern relates to approval of dosage levels of Category I active ingredients in excess of the maximum effective dosage per dosage unit based upon sustained-release or timed-release characteristics of the particular product. The issue facing the Panel is whether to recommend that the drug application procedures or whether drug application procedures be approved for testing which can be included in the CCABA drug monograph. The Panel views the exclusive use of the new drug application procedures as eliminating any possible general recognition for timed-release products. The Panel is aware that the drug industry has developed appropriate test procedures for specific timed-release mechanisms which would assure that various timed-release products deliver an effective dosage of active ingredient over a claimed extended period of time between, e.g., 8 and 12 hours. The Panel recommends that 4 years be provided for the development of such test procedures. The Panel is concerned, however, that in the interim some product would be marketed with inadequate release claims which, due to poor formulation, would deliver unsafe or ineffective dosages of drugs to the consumer. To assure that safe and effective products are available to the consumer, the Panel recommends that, during this interim period while the drug industry is developing tests for the standardization of all OTC timed-release CCABA products, drug application procedures not be permitted in the labeling unless data have been presented before marketing to the Food and Drug Administration demonstrating that the timed-release preparation delivers the single therapeutic dosage by an amount sufficient to produce blood levels or other effects that approximate those achieved by multiple administration of smaller therapeutic dosage units at accepted intervals based on the absorption and/or excretion characteristics of the drug.

The Panel is concerned that after reviewing the safety and effectiveness of active ingredients, the timed-release formulation may modify the safety and ef-
fectedness in such a way that in essence these products will not be as safe or as effective as the Panel intends.

Any active ingredients or combination of active ingredients that include a claim for time-release or delayed release be placed in Category III unless appropriate data can be presented to the Food and Drug Administration as outlined above.

References


F. DEFERMENT OF "SORE THROAT" CLAIM

The term "sore throat" is used by consumers to describe a symptom frequently accompanying cough, nasal congestion, or the symptom complex of the "common cold." Sore throat appears an indication or a quality of product included in submissions reviewed by the Panel.

Ingredients to which sore throat indications are attributed include, in general, local anesthetics and antibiotics. The Panel, working in conjunction with the Food and Drug Administration, has determined that the expertise for evaluating these ingredients for safety and effectiveness resides in the OTC Oral Cavity Panel and has therefore referred these ingredients and the "sore throat" indication and claim to the OTC Oral Cavity Panel.

The Panel notes, however, that while the sore throat may be due to simple irritation resulting from nasal congestion and consequent breathing through the mouth, it may also be due to an infection, with potential for serious complications. In the latter circumstances, the patient should not self-medicate and suppress the pain of cold with delay because delay in obtaining medical attention can have serious consequences. Labeling for products intended for relief of sore throat should emphasize that such products are for use only for "minor throat irritation."

The products should bear adequate warnings that they are not intended for persistent or chronic sore throat accompanied by fever or other symptoms like headache, rash, nausea or vomiting, or dizziness. The label should also indicate the potential seriousness of a sore throat and bear adequate instructions for obtaining medical consultation.

G. DRUG MISUSE AND ABUSE

Drug abuse, in its broadest sense, can be described as intentional consumption of a drug for reasons other than legitimate therapeutic uses, often in excess of normally acceptable doses and dosage intervals. Drug misuse generally refers to overuse of a drug for therapeutic purposes due to misinformation or ignorance about its rational use. To the extent that OTC drugs are able to suppress symptoms and through their pharmacological actions also affect other systems such as side effects, misuse and/or abuse of OTC products can be expected to occur. The Panel believes, however, that drugs having documented effectiveness, therapeutic utility, and abuse potential, particularly for self-diagnosable conditions in accordance with label instructions represent a valuable, national public health resource.

Misuse and abuse of drugs is an increasing problem in our society. The Panel is aware of this problem and has addressed it in a limited extent. Of those drugs reviewed by this Panel, the former exempt narcotics listed in Schedule V (21 CFR 1308.15), alcohol, sympathomimetics, and belladonna alkaloids appear to be most subject to abuse. It is not within the purview or charge to the Panel to evaluate the numerous psychological, sociological, or economic factors involved in drug abuse. Consequently, the following comments and recommendations are based on medical and scientific data related to safety and effectiveness of these OTC drugs.

The risk of misuse and/or abuse is minimized by restriction on the types of pharmacologic agents in available OTC products, limitations on concentration of active drug, and adequate and explicit directions for use coupled with appropriate warnings. The Panel also urges that all appropriate measures be directed to reducing the incidence and severity of accidental overdosage, including increased education of the consumer regarding storage of medications, limitations on quantities per product packages, and employment of safety packaging.

In general, OTC products that have been carefully formulated, thoroughly tested, and adequately labeled are safe when taken in accordance with label instructions for use and dosage. However, when these products are misused or abused, the potential for such unexpected, and/or toxic effects. Such drug abuse affects not only the individual himself, but society as a whole. The drug abuse problem is a complex one requiring the joint effort for solution by health care professionals, government, industry, educational institutions, and the public.

The Panel urges for a balance in educational programs directed to consumers, which illustrate not only the horrors of narcotic addiction, but also the beneficial properties of effective therapeutic agents. Their contribution to man's well-being, their undesirable side effects as well as the dangers inherent in all drugs if not properly used. The Panel believes that groundwork in drug abuse prevention be laid down for children at an early age and reinforced throughout their lifetimes.

There is, at this time, a conspicuous lack of data available on the nature and extent of misuse and abuse of OTC products. The Panel believes it is an obligation of the industry, government, and health care professionals to find out how these products, and especially potentially abuseable ones, are being used and misused. The Panel urges, therefore, and recommends attention be directed to definitive, properly conducted studies to provide an indication of the magnitude of the problem attendant to misuse and abuse of OTC products, especially those affecting the central nervous system.

1. Cephalalgia. During the time the Panel was in session, the Food and Drug Administration issued a proposed regulation in the Federal Register of September 12, 1973 (38 FR 18747) which proposed to place codeine-containing cough preparations on prescription by modification of 21 CFR 329.20.

At the present time, codeine-containing cough syrups are available for purchase OTC after the patient has signed a registry which records the consumer's name, amount purchased, intended use, and date of purchase. The proposed regulation would have eliminated the availability of codeine-containing cough preparations, making such preparations available only by a physician's prescription.

At the request of the Food and Drug Administration, the Panel reviewed the studies on the basis of which the Bureau of Narcotics and Dangerous Drugs (BNDD) (now the Drug Enforcement Administration) asked the Food and Drug Administration to revoke the OTC status and discuss these studies with representatives of the BNDD. In addition, the Panel discussed the potential for codeine abuse with representatives from Food and Drug Administration's Division of Neuropharmacological Drug Products and discussed with Food and Drug Administration officials aspects of the national policy concerning opium products and production.
As use in children of most drugs in asthmatic products and recommendcough, allergy, bronchodilator, and antitussive preparations on the basis of scientific and medical evidence alone, it is the Panel's opinion that codeine-containing cough preparations should continue to be available over-the-counter. The Panel recognizes, however, that in the case of children the Food and Drug Administration (removal of prescription exemption for such preparations), considerations go beyond questions of safety and effectiveness alone. The Panel does not deem it part of its function to evaluate factors which are not directly concerned with medical effectiveness. On the other hand, there appears to be a conflict between the findings regarding the basic safety and effectiveness of codeine and the removal of the prescription exemption, the Panel strongly urges that FDA clearly identify all factors which lead to FDA's final decision.

As a result, the Commissioner issued a notice to the manufacturers of OTC products, requiring them to state in the Federal Register of March 24, 1975 (40 FR 12998), that labeling claims for children under 2 years of age should be advised to consult a physician for diagnosis and individualized therapeutic recommendations, even for symptoms considered to be self-limiting. The Panel recognizes that the general labeling of CCABA products for use in children under 2 years of age requires the advice and supervision of a physician. The Panel concurs with accepted medical practice that recommends that children be administered a minimum amount of alcohol. Therefore, alcohol in pediatric formulations should be maintained at the lowest possible concentration. If pharmaceutically possible, products should be formulated without alcohol. Therefore, the Panel recommends that CCABA products containing an alcoholic content greater than 10 percent (weight/weight) should not be given to children under 6 years except under the advice and supervision of a physician.

In the recommendation of the Special Panel on Pediatric Dosage, the Panel recommends that the general labeling of CCABA products for use in children under 2 years of age be derived from data obtained in clinical trials with children using protocols similar to those of adult patients. The Panel recognizes the extreme difficulties attendant upon such trials but also recognizes the immediate need to make recommendations for pediatric dosage pending availability of such definitive data.

Traditionally, pediatric dosage calculations for infants and children have been based on body surface area, weight, or age of the child as a proportion of the "usual adult dose." Dosage calculated on the basis of the age of the child, although convenient, may be the least reliable method of calculation in view of the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the Panel has recommended dosage recommendations based on age as the most reasonable since they would be most easily understood by the consumer. In order to provide the needed dosage recommendations for pediatric patients, the Panel sought the assistance of a panel of experts in pediatric drug therapy. This Special Panel on Pediatric Dosage was convened and met concurrently with the Panel on November 1, 1974 and made recommendations:

- Charles Jancewsky, M.D.
- Sumner Taffee, M.D.
- Jennifer Logan, M.B., B.Ch.
- G. Warren Bierman, M.D.
- Louis G. Linarelli, M.D.
- Vincent D. Lurkin, M.D.
- Constantine Falliers, M.D.

Subsequently, the Special Panel on Pediatric Dosage conducted correspondence and review of all pediatric dosage recommendations. These recommendations have been considered in the preparation of this document. Unless indicated contrarily, the Panel recommends the following guidelines for determining safe and effective pediatric dosages for the Individual CCABA ingredients discussed in this document: For infants under 2 years of age, the pediatric dosage should be established by a physician. For children 2 to under 6 years of age, the pediatric dosage is 1/4 the adult dosage; for children 6 to under 12 years of age, the dosage is 1/2 the adult dosage.

The Panel has determined that the labeling terms "baby" and/or "infant" on CCABA products implies that such products have been approved for use in children under 2 years of age. The Panel recognizes that CCABA products exclude from their labeling the imprudent terms "baby" and/or "infant" unless the ingredient(s) has been specifically demonstrated as safe and effective for children under 2 years of age. In addition, products shown to be safe and effective for children under 2 years of age must provide specific dosages in their labeling. Furthermore, the Panel considers the advisability of including them in drug products be reviewed by an appropriate body. Since many of these products are used in the formulation of many drug preparations. By placing these preparations in a "prescription only" category, their use would be severely reduced and thus the market for imported products was reduced. In addition, BND had performed several studies that seemed to indicate a high incidence of abuse of codeine-containing cough preparations, possibly due to the ease of buying and contributing to the illicit drug traffic.

After reviewing all pertinent scientific data, the Panel concluded that codeine and its salts are safe and effective for OTC use as antitussives when used in accordance with instructions on the label. The potential for abuse of codeine is viewed by the Panel as negligible. When codeine is used, caution is found necessary because of the potential for dependence. Although codeine can partially suppress morphine withdrawal, it may require high doses in the range of 1,500 to 1,800 mg per day given by injection.

The Panel forwarded to the Commissioner the following statement:

- Alcohol abuse. Alcohol, in concentrations up to 42 percent, i.e., 64 proof, is present as a vehicle in a variety of OTC products reviewed by the Panel. The Panel recognizes a potential for abuse of alcohol contained in OTC cough, cold, allergy, bronchodilator, and antihistaminic products and recommendations directed to educational programs and need for studies to determine the incidence and severity of misuse and abuse of drugs apply equally to abuse and misuse of alcohol.

H. Pediatric Dosage

The Panel is aware that data on the use in children of most drugs in CCABA products are negligible or nonexistent. Yet, parents are concerned about the potential for therapeutic effects in a particular patient, adult or child, is dependent upon factors such as the drug itself, individual patient variables such as special sensitivity or tolerance to the specific agent, age of patient, hereditary factors, and other psychologic or psychological conditions. Children's dosage calculated by any method that does not take all of these variables into account, therefore, can only be considered rough estimates.

Definitive pediatric drug dosage should be derived from data obtained in clinical trials with children using protocols similar to those of adult patients. The Panel recognizes the extreme difficulties attendant upon such trials but also recognizes the immediate need to make recommendations for pediatric dosage pending availability of such definitive data.

Traditionally, pediatric dosage calculations for infants and children have been based on body surface area, weight, or age of the child as a proportion of the "usual adult dose." Dosage calculated on the basis of the age of the child, although convenient, may be the least reliable method of calculation in view of the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the Panel has recommended dosage recommendations based on age as the most reasonable since they would be most easily understood by the consumer.

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Members of the Pediatric Panel were:

- Charles Jancewsky, M.D.
- Sumner Taffee, M.D.
- Jennifer Logan, M.B., B.Ch.
- G. Warren Bierman, M.D.
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PROPOSED RULES

products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to OTC products.

For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. These reasons may be allergic reactions, idiosyncrasy, fear of safety (whether valid or not), or personal dislike. It is impossible to make a free choice in this regard unless the full contents of drug products are listed on the label. Therefore, this Panel strongly recommends that the Food and Drug Administration require full ingredient labeling of inactive as well as active ingredients in descending order of quantities present in all drug products. In support of this position the Panel notes that food products are already required to have such labeling, and since the purpose of a drug is to alleviate symptoms of disease, it would seem much more compelling to have this information on all drugs.

In line with the Panel's desire to expose the consumer to a larger number of ingredients possible, the Panel has previously recommended that marketed products contain only those ingredients essential to the product. (See part II, paragraph C.2 above—Identification of Ingredients in Combination Products.) Although chloroform was reviewed, and considered by the Panel to be an inactive ingredient, it was reviewed again at the special request of the Food and Drug Administration, because of reports suggesting that it is carcinogenic (Refs. 1 and 2). A discussion can be found in this document. (See part IV, paragraph B.2.b below—Chloroform.)

REFERENCES


(2) OTC Volume 649338.

J. ADVANTAGES OF SINGLE INGREDIENT PRODUCTS

OTC drug combination products seem to provide the public with many options from which to select the preparation most likely to relieve a symptom or group of symptoms. The combinations available would seem on the surface to be rational. The Panel has discussed CCABA combination products earlier in this document. (See part II, paragraph C.1 above—General combination policy.) However, the individual may need to tolerate or choose from the combination most likely to relieve symptoms of disease. In the combination product and the presence of the others may be unnecessary or, because of side effects or idiosyncratic reactions, their presence may preclude use of the combination.

Great variability with regard to side effects induced by drugs is seen among patients. Common examples are dryness causing any antibiotic of the ingested materials, feedlessness and sleeplessness caused by ephedrine. Furthermore, the ratio in which the components exist in the combination will be unacceptable for some persons. Although these effects and the drugs producing them are familiar to physicians and pharmacists, the public is unlikely to identify the ingredient causing the side-effect if the ingredient is present in a combination. This difficulty is largely avoided with single ingredients, which many physicians prefer to prescribe. With a single ingredient, whether available in a drug or on prescription only, the patient can observe the drug's action with relative ease and can adjust the dosage according to need. Experience gained in this way could be very useful to a patient on occasions of future need for self medication.

Single ingredients are rarely available among CCABA OTC drugs. Since many physicians prefer to treat with single ingredients, it seems logical for the public to have the option to medicate themselves with single ingredients also.

In summary, availability of individual ingredients would provide increased opportunity for the public to evaluate OTC drugs and allow the public to avoid taking two or more drugs where one might suffice. It seems more logical and possibly safer self-medication.

It is strongly recommended therefore, that any active ingredient marketed in OTC preparations for cold, cough, etc. be specifically named in the label and in a form equally convenient to administer.

K. ADVERTISING

The Panel is aware that the role of the Food and Drug Administration is to regulate labeling of over-the-counter drugs and the role of the Federal Trade Commission is to enforce adherence to such labeling in advertising. In addition to recommending specific labeling claims, warnings, and dosages, the Panel would like to make some general comments and recommendations regarding advertising of drugs.

Advertisements extend the label beyond the pharmacist's counter or medicine cabinet. The public may well receive most of its attitude toward CCABA remedies from advertisements—particularly television advertisements.

For this reason the Panel strongly urges the Federal Trade Commission to challenge any advertisement which:

1. In any way negates or dilutes the information on the label, especially the contraindications.

2. Suggests or leans heavily on words, phrases, and portrayals that lead the lay person to assume that the product is to be used in any manner not recommended in the monograph established below, or that it cures when in reality it only alleviates symptoms.

The Panel further recommends that advertisements for CCABA remedies not be placed where children may see or use the product. The Panel strongly urges the Federal Trade Commission to challenge any advertisement which:

1. In any way negates or dilutes the information on the label, especially the contraindications concerning child use.

L. STATEMENT ON CCABA COMBINATION PRODUCTS CONTAINING ASPIRIN

The Panel is aware that certain individuals develop manifestations simulating an allergic reaction within 15 to 45 minutes after taking 300 to 600 mg of aspirin (acetylsalicylic acid) (Ref. 1). Such reactions may occur in individuals who have previously been well tolerated by these individuals for many years. The major manifestation of such an allergic type reaction to aspirin is asthma, which is usually not recognized as the cause of
the reaction until such episodes occur once or twice more.

The association between nasal polyps, asthma, and aspirin sensitivity has been recognized for many years, and there are many reports in the literature (Refs. 1, 3, and 9). Eosinophilia is the rule in these patients and this should be considered as part of the syndrome. The yellow dye, tartrazine, and the anti-inflammatory drug indomethacin, are also reported to cause asthma in these patients (Ref. 9).

The Panel recognizes that prevention is the best course of action, which includes recognition of the syndrome and proper instruction given to the patient. However, the Panel notes that the presence of aspirin in combination with other drugs can lead to ingestion of aspirin by error, a point frequently made by patients. Furthermore, the first reaction of this kind in aspirin-sensitive individuals will occur more often than would occur if aspirin were only available as a single ingredient.

The OTC drugs under review by the Panel are frequently taken by consumers in whom aspirin is used in varying quantities. For this reason the Panel concludes that the availability of aspirin in combination with other drugs can be expected to lead to ingestion of aspirin by error, a point frequently made by patients. Furthermore, the first reaction of this kind in aspirin-sensitive individuals will occur more often than would occur if aspirin were only available as a single ingredient.

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ceved premarket clearance through a New Drug Application (NDA) for safety prior to 1972. The Panel in reaching its decision on the study of each of these drugs, and to decide if any drug or combination of drugs is effective, a number of procedures were employed. These procedures have been included in the "Data Required for Evaluation" sections following the ingredient(s) of each pharmacologic group.

A. New Drug Applications

The utilization of the pressurized, self-contained and self-propelled "aerosol" dosage forms in delivering pharmaceuticals was begun in the 1950's when advances in propellant technology, techniques in aerosol valves, and containers made possible the accurate delivery of metered doses for direct inhalation into the respiratory system. Development in the areas of fine particle technology and different aerosol systems kept pace with the evolution of specialized valves and actuators, containers of diverse materials such as glass, coated metals and plastics, and a variety of propellant gases such as the halocarbons, compressed gases (nitrogen, carbon dioxide, nitrous oxide), and hydrocarbon gases (butane, isobutane, pentane). The Panel is aware of the advantages and disadvantages of the pressurized drug products that were the subject of submissions to the Panel. Among the advantages may be listed:

1. Aerosol products are permanently sealed units, and thus their contents are maintained in a stable form that is protected from accidental contamination by organisms, atmospheric gases, moisture, and sunlight that are sometimes encountered with the use of ordinary containers that are repeatedly opened.

2. The utilization of specialized valves and adapters permit the release of mists, sprays, or true aerosols (particles suspended in gas), in a controlled manner that assures the rapid administration of the aerosolized drug. This is particularly useful when prompt onset of action is desirable.

3. Metering valves and containers are available in compact form, so as to permit the consumer to carry the product on his person with little inconvenience and with quick accessibility when medication is required.

4. Aerosol products designed to emit an intermittent or continuous spray of medicaments into the atmosphere of a patient's room or into aerosolized mists containing particles that are fine enough to be inhaled and thus exert their effect rapidly in the respiratory tract.

In recent years the advantages of the aerosolized forms of treatments for drug delivery of bronchial asthma and the transitory symptoms of the "common cold" have been challenged because of potential toxicities. These include the cardiotoxicity of the halocarbon propellant, fluorocarbon 11. Several studies have been reported that indicate the propellant can be absorbed into the blood with a persistence of a small quantity in the blood after 1 hour. Reports of accidental sudden deaths following the inhalation of aerosols imply the potential for an abuse that cannot be overlooked.

B. Propellant Gases

More recently predictions based on the use of computer models have warned about the possibility that halocarbons released into the air from aerosol products may be the cause of major ozone layer in the stratosphere. Concern has been expressed that these predictions are accurate and the protective layer of the stratosphere against ultraviolet radiation may become impaired.

The Panel, therefore, concludes that although aerosol products do possess inherent advantages for specialized application of drugs in bronchial asthma and other respiratory conditions, the possibility of toxic effects of the halocarbon propellants should be carefully evaluated by a suitable Panel of experts in this area.

C. OTC Product Labeling Claims Not Supported by Scientific Evidence

The Panel has reviewed the submitted labeling claims made for CCABA products. It is interesting to note that products for relief of symptoms of the "common cold" and allergies are probably the largest category of OTC drug products on the United States OTC drug market. In fact, there are estimates by the Food and Drug Administration that as many as 50,000 different OTC CCABA drug products are currently marketed. Because of this vast array of products, the consumer is often faced with a myriad of confusing claims, which are not only vague and hard to comprehend, but also make it almost impossible for the consumer to distinguish between these products.

One of the primary functions of this Panel is to minimize this confusion by clarifying the labeling. In that way the ordinary individual who purchases an OTC drug product for the relief of symptoms, etc., of the "common cold" or allergies, will understand exactly what the product will do for him, the limits of the product's capability, and the conditions under which the product should be used. In this way the consumer will be able to distinguish between various CCABA products. The Panel believes that at the present time this is not possible since the labeling that appears on many currently marketed CCABA products tends to be overly complicated, vague, unsupported by scientific data, and in some cases is false and misleading.

The Panel understands the drug industry's desire to market OTC drug products for the relief of symptoms of the "common cold" or allergies by suggesting uniqueness or superiority of one product over another. But uniqueness or superiority must be proven scientifically or labeling will mislead and unduly confuse the consumer. For example, if one ingredient can be demonstrated to be superior to another because of greater effectiveness, then the consumer should be so informed. Conversely, if two ingredients are indistinguishable with regard to effectiveness, etc., both are equally
effective in suppression of cough, then it is misleading to claim superiority for one of the ingredients. In this regard, the Panel wishes to make clear that its function is not to consider ingredients in order to determine the OTC drug of choice. Rather, the Panel determines only safety and effectiveness for active OTC CCABA ingredients, as well as proper dosage ranges for drugs containing combinations of appropriate ingredients. In reviewing the scientific literature for CCABA ingredients, it is clear that ingredients of the same pharmacologic group that are Category I, i.e., generally recognized as safe and effective, have similar effectiveness in the dosage ranges recommended. Consequently, the Panel concludes that all claims which imply superiority of one product over another, both of which contain Category I ingredients in the same pharmacologic group, should be prohibited from the labeling of CCABA products. These claims would include such phrases as "Superior to ordinary" and "Specially Improved or selected ingredients". In addition, the Panel has determined that statements to the effect that a product is "extra strength" or "contains more active ingredient per dose," are also misleading unless fully substantiated. Thus, the Panel has found no justification for claiming more activity per dose for one Category I ingredient over another because there is no scientific merit from a therapeutic point of view between a product containing 15 mg of a drug A and another containing 30 mg of drug B if they are similarly effective. Unsubstantiated claims for "extra strength" or "contains more active ingredient per dose" or "higher dose level" or "stronger than" are therefore misleading. However, assuming that claims of greater potency were based on documented facts, such increase in potency might also indicate an increase in the potential side effects. Under such circumstances the Panel feels that such claims are misleading to the consumer.

Misleading superiority claims may also manifest themselves as claims that state or imply actions peculiar to a particular product, when in fact those claims are applicable to all OTC drug products or all Category I ingredients of the same pharmacologic group. Thus, for example, if two different OTC cough products contain different ingredients of the same pharmacologic group, this would be misleading to make such claims as "specially formulated" or "specially selected ingredients". This view would, of course, also be applicable to combinations of appropriate CCABA ingredients or combinations of CCABA and non-CCABA ingredients. Thus, claims such as "teamcd components would be considered misleading by the Panel.

Another area of concern to the Panel is claims implying a unique physiological action that no scientific evidence or foundation or meaning for will be meaningless to the consumer. Such claims include pseudo-medical terms such as "antiallergic" or pseudo-medical activities such as "fights", "wakes up", and "multiaction". Some claims mislead the consumer into believing a product has a unique action, when in fact that pharmacologic action is shared by all similar OTC drug products containing ingredients from the same pharmacologic class. Examples include claims that an ingredient "travels through the bloodstream" or "works internally." All drugs taken internally "work internally" and virtually all drugs taken internally are absorbed into the bloodstream. Thus, these claims are also not appropriate in OTC labeling.

The Panel has made a clear distinction in this document between the treatment for the relief of the symptoms of a disease, e.g., cough, runny nose and the treatment of the disease itself, e.g., "common cold." With few exceptions, CCABA products are indicated only for the treatment for the relief of symptoms. The most common disease associated with CCABA products is the "common cold." The Panel has discussed this respiratory disease earlier in this document. (See part II, paragraph B.I. above—The "common cold.") The Panel concludes that "there is no demonstrated safe and effective OTC active ingredient or combination of active ingredients acceptable for specific treatment of the "common cold."

Consequently, the Panel recommends that product names or labeling claims that infer or suggest a direct relationship to the "common cold," e.g., "cold medicine," "cold formula," "for relief of colds," should not be allowed. Such statements may mislead the consumer into believing that these products protect, treat, or cure the disease itself. The active ingredients reviewed by the Panel and included in currently marketed CCABA products are generally used for the treatment for relief of the symptoms of disease. The Panel concludes that if labeling is restricted to the proven pharmacologic activities of the active ingredients in CCABA products, reference to the specific activities of such ingredients in alleviating symptoms is acceptable. The Panel has summarized the commonly encountered symptoms and the knowledge and pharmacologic groups earlier in this document. (See part II, paragraph B. above—Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antihistamine Products.)

For drugs used to treat the symptoms of the "common cold," the Panel recommends that in addition to the acceptable claims (Category D) for specific pharmacologic activities, the following summary of indications may be used: "(symptoms) as may occur in the "common cold""). An example for a product containing an antitussive would be "For cough as may occur in the "common cold"." On the other hand, the Panel finds that certain OTC bronchodilator active ingredients are safe and effective for the treatment of asthma. This disease is essential for those individuals diagnosed by a physician as having the disease. This of course is acceptable, based upon the Panel's recommendations. In this document that the following warning be on all products containing bronchodilators: "Do not use this product unless a diagnosis of asthma has been made by a physician". (See part V, paragraph B.1 below—Category I Labeling.)

The Panel also recognizes that allergic rhinitis (such as hay fever) is a very common disease. Unlike the "common cold," most affected individuals understand the etiology of such a disease and realize that it cannot be prevented or cured by OTC antihistamines or nasal decongestants. However, in cases with asthma, the manifestations of this disease can be treated with such a product. Here again, it is the Panel's conclusion that it is also acceptable for the terms "hay fever", and "allergic rhinitis", to appear in labeling of products containing active ingredients either as part of a product name, e.g., hay fever medicine, or appearing alone in labeling claims, e.g., "Dries running nose as may occur with allergic rhinitis", or "For treatment of hay fever".

Q. INGREDIENT EQUIVALENCE

The Panel recognizes that the ingredients submitted and reviewed may exist in the same chemical forms or in the same combination as the same active ingredients. The Panel notes that other salts, esters, and complexes of these ingredients may be available, which may be therapeutically equivalent to the forms of the ingredients considered by the Panel. In recognition of this fact, the Panel concludes that provided that there are suitable data to indicate that the salt, ester, or complex is equivalent, the salt, ester, and complexes of ingredients dis-
cussed in the monograph would be ac-
sceptable. However, it is essential that the dosage used be equivalent to the dosage of the ingredient in the monograph.

Introduction to Pharmacologic Classifications
Not all CCABA products are used for the same purpose, nor should the requirements for effectiveness be the same. In an attempt to classify CCABA active ingredients and their products it was necessary to distinguish between the pharmacologic activities and resulting effectiveness for labeled claims of these products. The following classifications of CCABA products were developed by the Panel in an attempt to simplify categorization of ingredients and thereby eliminate labeling confusion:

Antitussives
Expectorants
Bronchodilators
Anticholinergics
Antihistamines
Nasal decongestants
Miscellaneous active ingredients

III. Antitussives
A. General Discussion

An antitussive agent specifically inhibits or suppresses the act of coughing. Direct inhibition may result from depression of medullary or higher centers in the brain; diminishing the sensitivity of the cough receptors in the membranes lining the throat and respiratory passages; interruption of the afferent (sensory) fibers that carry impulses to the brain or to the muscles that are involved in the act of coughing; and by removal of irritants and excessive secretions through the improvement in bronchial drainage.

In theory, cough suppression may be produced indirectly by one or two mechanisms: A soothing action on the irritated or inflamed throat, which would in effect decrease the sensitivity of special nerve endings or cough receptors in such membranes; and a relief of spasm or localized constriction of the airway. This is known as the "local anesthetic" effect following the inhibition of an irritant.

The Panel has followed the presently accepted medical approach and has classified antitussives according to their principal site of action.

1. Centrally acting antitussive agents produce cough suppression by acting on the central nervous system to depress the medullary (brain) cough center and thus raise its threshold for afferent (sensory) action of cough impulses to the brain; diminishing the sensitivity of the brain cough center and, therefore, they would seem to be more advantageous for use in treating cough and also for use in individuals who seem psychologically predisposed to drug dependence.

In general, the antitussives available for OTC use are and should be designed to diminish coughs associated with acute, self-limiting conditions that cause irritation to the respiratory airway. Since it is highly unlikely that such conditions would persist for more than 1 week, the Panel has limited the period of administration of these antitussives to a maximum of 7 days. A persistent cough for more than 1 week or one accompanied by high fever, rash, or persistent headache may be indicative of a serious disease, which should be treated by a physician and does not lend itself to self-medication by antitussives. In children under 2 years of age, the Panel was unable to determine an OTC dose for this age group. Based upon the lack of available data, the Panel recommends the following warning for products containing antitussives: "Do not give this product to children under 2 years except under the advice and supervision of a physician."

Since a persistent or chronic cough may be a sign of a serious condition requiring medical intervention and should be brought to the attention of a physician, the Panel recommends that all labeling for antitussive products bear the following warning: "Caution: A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by high fever, rash, or persistent headache, consult a physician."

In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an overproduction of secretions which accumulates in the airway and results in productive cough. In these conditions the suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful.

References

Labeling
Consumers often have difficulty understanding the intended meaning of OTC drug labeling. The Panel has observed that the use of vague words which imply a greater effectiveness than other similar OTC products is false and misleading. The Panel has reviewed the labeling that was submitted for antitussives and for other pharmacologic groups and has attempted to explain why some labeling is acceptable, objectionable, or questionable.

In the case of antitussives, the Panel has reviewed the symptoms of cough and the mechanisms by which the pharmacologic response to cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material. As stated above, medications that suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. Based upon the previous discussion of cough and the discussion of antitussives, the Panel concludes that the following indications are acceptable labeling claims for generally recognized safe and effective antitussives (cough suppressants) for the temporary relief of cough: "Cough suppressant which temporarily reduces the impulse to cough.

For the temporary relief of cough and coughing due to minor throat irritation as may occur with the common cold or inhaled irritants.

Temporarily quiets coughing by its antitussive action". "Temporarily helps you cough less. Temporarily helps to quiet the cough reflex that causes coughing."

Because of the lack of clinical studies in children under 2 years of age, the Panel was unable to determine an OTC dose for this age group. Based upon the lack of available data, the Panel recommends the following warning for products containing antitussives: "Do not give this product to children under 2 years except under the advice and supervision of a physician."

D. Categorization of Data

1. Category I conditions under which antitussive ingredients are generally recognized as safe and effective and are not mislabeled.

Category I—active ingredients

The Panel has classified the following antitussive active ingredients as general-
ly recognized as safe and effective and not misbranded:

- Codeine preparations: Codeine, Codeine alka-
  loid, Codeine phosphate, Codeine sulfate
  Dextromethorphan
  Dextromethorphan hydrobromide
  Diphenhydramine hydrochloride

a. Codeine preparations: (codeine, co-
  deine phosphate, codeine sulfate)
The Panel concludes that codeine and its salts are safe and effective for OTC use as antitussives as specified in the dosage section discussed below.

(1) Safety. Side effects such as dryness,
  light-headedness, excitement, loss of appetite, nausea, vomiting, headache, abdominal discomfort and constipation with oral doses of 20 mg of codeine have not been significantly greater than with placebo (Ref. 1). The Panel has reviewed the literature and finds that respiratory depression may occur but is usually seen when codeine products are used as prescription medication with dose levels of 120 mg every 4 hours which results in the codeine having analgesic activity similar to that of 40 mg of morphine (Ref. 9). Such high blood levels could pose a real hazard in certain cases of respiratory disease associated with a tendency towards carbon dioxide retention. By central respiratory depression, this change of oxygen and carbon dioxide would be impaired and there would be a tendency for the carbon dioxide to accumulate in the blood resulting in or aggravating respiratory acidosis with a dulling of the senses progressing to coma. As little as 60 mg of codeine in adults has produced measurable respiratory depression, judging from carbon dioxide response curves (Refs. 3 and 4). This has not been apparent with the doses approved for OTC use. In an infant, doses of 10 mg every 2 hours for 10 doses has led to deep coma (Ref. 5). Death has occurred from overdose with codeine in the range of 375 to 1,750 mg but effects were complicated by the presence of other central nervous system depressants (Ref. 9).

The Panel believes the potential for abuse of codeine is negligible (Refs. 7, 8, and 9). It is further the opinion of the Panel that under usual conditions of nonnarcotic active medicinal ingredients occurring from overdosage with codeine in codeine over-the-counter. These regulations (Refs. 5 and 6) also have been used to demonstrate the effectiveness of codeine as an antitussive in dose ranges of 15 to 30 mg.

There are no well-controlled studies on the antitussive activity of codeine in children, and hence, dosage recommendations in children have been based on the general experience of the Pediatric Panel, which reviewed these recommended dosages. (See part II paragraph H. above—Pediatric Dosage.) Because the majority of clinical trials have been in children, it is generally accepted that the effectiveness of codeine in coughs due to upper respiratory infection may, in large measure, be extrapolated from the information on antitussive activity in chronic cough. This is further supported by an extensive clinical experience with the use of codeine over the past 50 years.

Because of abuse liability of codeine if available as a single ingredient in unlimited supply, the Panel concurs with the present Drug Enforcement Agency regulations, which limit the sale of codeine over-the-counter. These regulations limit the amount of codeine or its salts contained in an OTC product to 200 mg per 100 ml for liquid preparations or 100 mg per 30 g of other forms (21 CFR 1308.15(b)(1)). These regulations further specify that codeine for OTC purchase must include one or more non-narcotic active medicinal ingredients in sufficient proportion to confer medicinal qualities upon the product other than those possessed by codeine alone (21 CFR 1308.15(b)). In addition, these regulations limit OTC sale of the codeine containing products to quantities not exceeding 120 ml or 24 dosage units (21 CFR 1306.33(b)).

Dose: Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommendation for dosage except under the advice and supervision of a physician.

(4) Labelling: The Panel recommends the Category I labeling for antitussive ingredients. (See part III paragraph B.1 below—Category I Labelling.) In addition, the Panel recommends allowing specific labeling claims referable to a central mechanism of action:

(i) Indications. "Calms the cough control centers of the brain.

(ii) Warnings. "May cause or aggravate constipation."

”). (Do not give this product to children taking other drugs except under the advice and supervision of a physician.

(3) May not be taken by the patient if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician.

REFERENCES


(16) Eddy, W., F. J. P. McCoy and J. P. Colmore, "Does Response to Codeine in

b. Dextromethorphan, dextrorotatory dextrorotator isomer of the morphinan dextrorotator v isomer of the morphinan (Ref. 1). With usual antitussive doses, no effect has been noted on respiration, the cardiovascular system, or the gastrointestinal tract. With very large doses such as occur with abuse or accidental poisoning, respiratory depression has been noted (Refs. 2 and 3). However, no fatalities have been reported, even with doses in excess of 100 times the normal adult dose. Abuse has been reported by Degkwitz (Ref. 4) with doses of 300 to 1,500 mg several times daily, resulting in intoxication with bizarre behavior but no physical dependence.

(3) Effectiveness. Dextromethorphan is an active antitussive comparable to codeine on a mg-for-mg basis for cough suppression. Studies involving many species of animals and many methods for inducing cough have demonstrated that effectiveness of dextromethorphan as an antitussive is comparable to codeine (Refs. 5, 6, 7). In studies (Refs. 8 and 9) reported that dextromethorphan was less effective than codeine in equivalent doses. It has been demonstrated that dextromethorphan blocks central (brain) inhibition of incoming cough stimuli (Refs. 10 and 11).

There have been a large number of studies in man over the past 20 years. These have consisted of: Experimentally Induced cough with controlled double-blind crossover designs (Refs. 12 through 15) in which all but one (Ref. 13) showed effective antitussive activity; controlled subjective studies in pathologic coughs (Refs. 13, 16 through 18); controlled objective studies in pathologic cough (Refs. 19 and 20); and uncontrolled subjective studies in patients with acute cough resulting in cough (Refs. 21 and 22).

The wide range of safety and low order of toxicity in clinical trials has been documented by Ralph (Ref. 21). The lack of addiction liability has been confirmed recently by Mansky and Jasinski (Ref. 23).

The majority of these clinical studies demonstrate effective antitussive activity. Even though a few of the studies questioned the effectiveness of dextromethorphan. the Panel concluded that the effective dextromethorphan is generally recognized as effective, and because of its low order of toxicity it is probably the safest antitussive available.

(3) Dextromethorphan dosage is 10 to 20 mg every 4 hours or 30 mg every 8 hours not to exceed 120 mg in 24 hours. Children 6 to 12 years oral dosage is 8mg to 10 mg every 4 hours or 20 mg every 8 hours not to exceed 60 mg in 24 hours. Children 2 to 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. below—Category I Labelling.)

(5) "Non-narcotic cough suppressant for the temporary control of coughs."

(6) Calms cough impulses without narcotics.

REFERENCES


c. Diphenhydramine hydrochloride. The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antitussive as specified in the dosage section discussed below.

(1) Safety. Diphenhydramine was the first of the antihistaminic agents developed in the U.S. and was first used in 1946, clinically, for the relief of a wide variety of allergic symptoms. Diphenhydramine had a limited number of laboratory animals combined with a high degree of antihistaminic action. The Panel reviewed a number of studies contained in the submissions (Refs. 1 and 2) and concluded that the action of sedation, adverse effects have been rare and the drug is safe. The Panel has also found the drug to be safe for use...
as an antihistamine and this use is discussed elsewhere in this document. (See part VII, paragraph B.1.c, below—Diphenhydramine.)

Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Ref. 3). A double-blind controlled study, in 29 patients, evidence of interference with tests for memory, rotary pursuit, or reaction time with diphenhydramine hydrochloride in doses of 12.5 and 25 mg every 4 hours (Ref. 4) on a double-blind controlled subjective study on 546 patients with acute upper respiratory infection, drowsiness was reported in 11 of 269 patients receiving 25 mg diphenhydramine a time daily for a 3 day period (Ref. 5). Two of 277 patients receiving placebo also reported drowsiness. In infants, high doses of diphenhydramine may cause excitation and convulsions (Ref. 1). The acute toxicity of diphenhydramine in a variety of animal species is similar to other antihistamines such as pyribenzamine. To children under 30 mg every 4 hours (Ref. 6) 30 tables or capsules containing 50 mg each may represent a lethal or near lethal dose (Ref. 3).

The Panel has recommended specific warnings because an asthmatic-like effect is described by patients which includes a drying sensation of the mouth and nose and difficulty with urination in patients with enlarged prostates.

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep-Aid Drug Products and published in the Federal Register of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little or no evidence of tolerance or habituation. The Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antihistamine and as a sleep-aid, are not recognized as being abusive by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industrialized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described herein. It is a central nervous system alpha-2agonist and its nonnarcotic designation: (i) Indications. (a) "Calms the cough control center and relieves coughing." (b) "May cause excitability especially in children." (c) "Do not take this product if you have pneumonia or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician." (d) Warnings. (a) "May cause marked drowsiness..." (b) "May cause excitability especially in children." (c) "Do not give this product to children under 6 years except under the advice and supervision of a physician." (d) "Do not give this product to children under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 37.5 mg in 24 hours."

REFERENCES

(4) OTC Volume 040224.
(8) Ferguson, H. C., "Personal Communication," Reference from Presentation to the FDA Review Panel on Over-The-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040228.
(11) Bickerman, H. A., "Evaluation of the Antitussive Activity of OTC-194, CT-235 and CT-260 Using Citric Acid Aerosols to Induce..."
Cough in Healthy Human Subjects,” Reference from Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040258.

(3) “An evaluation of the Antitussive Activity of 3 Liquid Preparations Employing Citric Acid Challenge to Elicit Cough in Healthy Subjects,” Reference from FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040258.


(18) Brumby, W. E., “Final Summarization and Evaluation of Data from Protocol MDN/303,” Reference from Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040258.

Category I Labeling

The Panel recommends the following Category I labeling for antitussive active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. Indications. (1) “Cough suppressant which temporarily reduces the impulsion to cough.”

(2) “For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold, or as may be incurred by inhalation of irritants.”

(3) “Temporarily quieting coughing by its antitussive action.”

(4) “Temporarily helps you cough less.”

(5) “Temporarily helps to quiet the cough reflex that causes coughing.”

b. Warnings. (1) “Do not give this product to children under 2 years except under the advice and supervision of a physician.”

(2) “Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician.”

(3) “A persistent cough may be a sign of serious condition. If cough persist for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent (4) “Temporarily helps you cough less.”

(5) “Temporarily helps to quiet the cough reflex that causes coughing.”

b. Warnings. (1) “Do not give this product to children under 2 years except under the advice and supervision of a physician.”

(2) “Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician.”

(3) “A persistent cough may be a sign of serious condition. If cough persist for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent (4) “Temporarily helps you cough less.”

(5) “Temporarily helps to quiet the cough reflex that causes coughing.”

b. Warnings. (1) “Do not give this product to children under 2 years except under the advice and supervision of a physician.”

(2) “Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician.”

(3) “A persistent cough may be a sign of serious condition. If cough persist for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent
Since no safe oral dose has been established for effective use as an antitussive, the Panel concludes that turpentine oil should not be available for oral OTC use as an antitussive. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or orally for other uses. Therefore, there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an antitussive. (Care part III, paragraph B.3.1. below—Turpentine—oils of turpentine (topical/inhalant).)

(2) Effectiveness. Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 2). There is no evidence to support its effectiveness as an antitussive when taken orally. (3) Evaluation. The Panel is unable to determine a safe oral dose for turpentine oil for use as an antitussive. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might be expected. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an antitussive.

References


Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II, paragraph C. above—OCTA Product Labeling—Use of Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance is acceptable. Unsustainable claims for antitussive include any statement containing the term "coughs", "which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", "natural", "extracted", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Statements alluding to greater potency, such as "extra strength" or "contains more antitussive per dose" are misleading because there are no acceptable controlled studies documenting that one preparation is more potent than another, particularly for Category I drugs. There is also no justification for claiming more antitussive per dose because there is no scientific merit from a therapeutic point of view between 15 mg of drug A and 50 mg of drug B if they are the same active ingredient. Therefore, the Panel concludes that all such claims are misleading to the consumer. Claims implying a physiological effect that either has no foundation or meaning will be meaningless to the public are unacceptable; such as, "gets to the roots of", "recommended by doctors", "travels through the blood stream", "works internally.

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable; such as, "fast" and "quick".

Statements such as "a dramatic advance", "the greatest advance in cough relief", "the modern way to stop coughs" etc., are vague generalizations, which do not establish" categories usefulness. The statements are unsupported by scientific evidence, and since they are meaningless, can only have the effect of misleading the consumer.

The Panel concludes that such labeling should be removed from the market until scientific testing supports their use.

3. Category III Conditions for which the available data are insufficient to permit final classification at this time. The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 4 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is under way. Adequate testing data are not obtained within 4 years, however, the ingredients and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as an antitussive must be demonstrated by controlled objective studies employing cough-counting techniques. Subjective data, alone, are unacceptable because of the marked variability in the subjective awareness of coughs. Studies have shown (Refs. 1 and 2) that there is a poor correlation in the subjective appreciation of the effectiveness of the cough suppressant and the actual objective studies done by employing cough-counting techniques.

References


ence in dose (3.29 mg/lozenge, 8 doses/ daily) appears illogical, and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) **Proposed dosage.** Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. For children under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) **Labeling.** The Panel recommends the Category I Labeling for antitussive active ingredients. (See part IV, paragraph B.1 above—Category I Labeling.)

(5) **Evaluation.** Data to demonstrate effectiveness as an antitussive will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

**Proposed Rules**

**References**


(4) OTC Volume 040289.


(6) OTC Volume 040285.

b. **Camphor (topical/inhalant).** The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant, but there are insufficient data to permit final classification of its 2.4 North Carolina for topical or inhalant OTC use as an antitussive.

(1) **Safety.** Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dose ranges used as an antitussive.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach, but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action, and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions. (Ref. 1). As little as 0.75 gm of camphor (equivalent to a teaspoonful of liniment of camphor or camphorated oil, which contain 20 percent camphor) has been fatal to children. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 3.5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could be fatal to a child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult, a dose up to 45 gm has been ingested with recovery. (Refs. 2 and 3).

(2) **Effectiveness.** There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant). The effectiveness of camphor is uncertain due to lack of properly controlled studies of the substance by itself.

Studies involving objective measurement of antitussive activity of camphor primarily involve mixtures of volatile substances topically applied as ointments (Refs. 3 and 4). as steam inhalations. (Refs. 5 through 7). and as lozenges. (Refs. 8 and 9). evaluated against artificially induced cough in normal subjects by the citric acid aerosol method. In these studies, significant antitussive activity is demonstrated for a mixture containing volatile substances camphor compared to placebo, but the contribution of the camphor component to this effect is not evident. In a crossover study involving 16 subjects, the effects of 5.3 percent camphor in a petroleum ointment applied to the chest of subjects were compared to an ointment containing several volatile substances in a mixed mixture of 5.3 percent camphor and to a placebo (petrolatum) in suppressing a citric acid aerosol-induced cough. The combination ointment contains camphor induced a significant decrease in cough counts just at the ½- and 1-hour intervals, whereas the single ingredient camphor ointment yielded a significant decrease in cough counts just at the ½- and 1-hour intervals averaging about 20 percent decrease in cough counts at the ½- and 1-hour intervals whereas the single ingredient camphor ointment yielded a significant decrease in cough counts just at the ½- and 1-hour intervals averaging about 10 percent decrease, and the petrolatum yielded no significant change in cough counts compared with base line (Ref. 3).

(3) **Proposed dosage.** Dosage for adults and children 2 to under 12 years is as follows:

- For adult use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and mouth to allow the vapors to rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.
- For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or wash basin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.
- For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) **Labeling.** The Panel recommends the Category I Labeling for antitussive active ingredients. (See part III, paragraph B.1 above—Category I Labeling.) In addition, the Panel recommends the following specific labeling:

- For topical ointment use: **Warning:** "For external use only. Do not take by mouth or place in nostrils."
- For steam inhalation use: **Warning:** "For steam inhalation only. Do not take by mouth."

(5) **Evaluation.** The Panel made the following recommendations:

- For topical ointment use: Data to demonstrate effectiveness will require only additional controlled cough counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C. below—Data Required for Evaluation.)
- For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C. below—Data Required for Evaluation.)
- For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C. below—Data Required for Evaluation.)

**References**


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(5) Packman, E. W., "Vaporub, Antitussive Screening: Citric Acid Aerosol Technique, CRD 74-19/A and B," Draft of unpublished data is included in OTC Volume 040289.

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(8) Packman, E. W., "Vicks Cough Drops, Antitussive Screening: Citric Acid Aerosol Technique, CRD 71-19/A and B," Draft of unpublished data is included in OTC Volume 040289.

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c. Caramiphen edisylate (caramiphen ethanedisulfonate). The Panel concludes that caramiphen edisylate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive. (1) Safety. Clinical experience has confirmed that caramiphen edisylate is safe in the single dose of 20 mg as an antitussive. Acute and chronic toxicity studies in animals indicate a wide margin of safety, and caramiphen was judged to be considerably less toxic than codeine (Ref. 1). Although caramiphen edisylate and drowsiness have been reported with dosage levels of 10 mg of caramiphen edisylate 8 times daily (Ref. 2). The incidence of these mild reactions increased as the dose was doubled, and one patient experienced a transient period of disorientation (Ref. 2). In a number of clinical trials, 12 of 172 patients reported adverse reactions, 4 of which were probably not drug related (Ref. 3). Although caramiphen pharmacologically is anticholinergic, with 1/2 to 5/6 the drying of the acetylcysteine mechanism (Ref. 4) which have been reported concerning its effect on bronchial secretions and no difficulty with retained secretions (Ref. 4). At the average dose of 10 to 20 mg 8 to 4 times daily toxic reactions have been reported. Reported side effects have included slight nausea, dizziness, and occasional drowsiness, which appeared to be dose related. Until additional experience has accumulated, the labeling warning below concerning glaucoma and enlarged prostate, which may cause a block to the flow of urine, is deemed necessary in view of the drug's anticholinergic properties (Ref. 4).

(2) Effectiveness. There are no well-controlled objective, clinical studies documenting the effectiveness of caramiphen edisylate as an antitussive. Studies in animals indicate that caramiphen is a centrally acting antitussive (Refs. 1 and 9). Cough suppression is due to an incenral blockage of the cough center for cough. Almost all of the reports of studies are uncontrolled, subjective clinical trials (Refs. 6 and 7). Two controlled studies with caramiphen edisylate showed that caramiphen to be significantly superior to placebo but slightly less active than codeine 15 mg (Refs. 8 and 9). The only well-controlled crossover study was performed by Abelmann, Gaensler and Badger (Ref. 2), who concluded that caramiphen was superior to placebo but not as effective as codeine or diphycodone none as a cough suppressant by subjective criteria, and that it decreased the amount of sputum in 61 percent of patients but without evidence of retention of sputum.

A controlled cough-counting study was recently reported in 25 patients with chronic cough (Ref. 10). The results of this study failed to show the efficacy of a single dose of 20 mg caramiphen as compared with placebo, hence, it was felt that no significant antitussive effect after the fourth and fifth doses of the drug. Because of a lack of information regarding the smoking habits of the subjects in this study, and no evidence to indicate that the high speed, automatic electronic counter is accurate and reliable by comparing it with actual cough counts, serious questions about the acceptability of this study are raised.

(3) Proposed dosage. Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years dosage is 5 to 10 mg every 4 to 6 hours not to exceed 40 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 10 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III paragraph B.I. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to a central mechanism of action and its non-narcotic designation: (1) Indications. (a) "Calms the cough control center and relieves coughing".

(b) "Helps calm nocturnal cough suppressant for the temporary control of coughs".

(c) "Calms cough impulses without narcotics".

(2) Warnings. (a) "Do not take this product if you have glaucoma or have difficulty in urination due to an enlarged prostate gland except under the advice and supervision of a physician".

(b) "Caution: Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(5) Evaluation. Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with cough due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III paragraph C. below—Data Required for Evaluation.)

References
(3) "Clinical Use of Torny," Collection of published and unpublished data is included in OTC Volume 3.
(5) Chakravary, N. C., M. Malalana, R. Jenson and H. L. Borton, "Clinical Effects of Antitussive Drugs on Cough and Respira-

b. Carbperpantene citrate. The Panel concludes that carbperpantene citrate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

Studies in several animal species revealed a low order of toxicity, which was comparable to codeine phosphate (Ref. 1). Intravenous administration resulted in slight transient falls in blood pressure with no effect on respiration. In addition, carbperpantene possesses marked anti spasmodic (relieves spasms) activity with weak anticholinergic (atropine-like) and local anesthetic properties. These results in dogs consisted for the most part of mild dryness of the mouth (Ref. 2). In this study, nine of 39 patients reported this side effect. An additional 10 complained of severe nausea and loss of appetite and discontinuation medication. At an average dose of 25 mg 4 times daily, few side effects have been reported, and have shown no evidence of dryness of the mouth. On the whole, this antitussive effect was mild and did not interfere with spurt production (Ref. 3), but the labeling warning (see below) concerning glaucoma and enlarged prostate is deemed necessary because of the anticholinergic properties of carbperpantene.

d. Effectiveness. There are no well-controlled studies documenting the effectiveness of carbperpantene citrate as an antitussive.

Animal studies employing a variety of methods for experimentally induced cough as well as pathologic cough in dogs indicate that the onset of action and duration of cough suppression is equivalent to codeine (Refs. 1 and 9), but in a review of the literature (Ref. 4) there was considerable disagreement as to carbperpantene's relative antitussive potency as compared with codeine. Clinical studies were all subjective in type and only one had a placebo control (Ref. 6). At doses ranging between 7 and 5 mg 3 to 4 times daily, most investigators have reported "good" to "excellent" antitussive effect. Most of the clinical trials were of short duration in acute respiratory conditions and were uncontrolled (Refs. 3, and 7 through 9). The Council's review of the data (Ref. 10) has concluded that, "available clinical evidence suggests that the effectiveness of the drug is limited to the acute (short duration) type of cough. Further and better controlled observations are necessary."
needed to establish its clinical useful-
ness" (Ref. 10). However, other investi-
gators (Refs. 3, 11, and 12) have found
alcathetin to be effective in all types of
cough. In one study, carbetapentane
was not as effective as codeine for severe
(intense and frequent) cough (Ref. 13).
None of these clinical studies employed
objective clinical measures to evaluate
effectiveness and few were adequately
controlled.

(2) Proposed dosage. Adult oral dosage
is 15 to 30 mg every 4 to 6 hours not to
exceed 180 mg daily. Children 6 to
under 12 years oral dosage is 7.5 to 15
mg every 4 to 6 hours not to exceed 90 mg
in 24 hours. Children 2 to under 6 years
dosage is 3.75 to 7.5 mg every 4 to
not exceed 45 mg in 24 hours. For children
under 2 years, there is no recommended
dosage except under the advice and
supervision of a physician.

(4) Labelling. The Panel recommends
the Category I labeling for antitussive
active ingredients. (See part III, para-
graph B.I. above—Category I Labelling.)
In addition, the Panel recommends the
following specific claims referable to a
central mechanism of action and its non-
habitual designation: (i) Indications.
(a) "Calm the cough control center and
relieves coughing".
(b) "Non-narcotic cough suppressant
for the temporary control of coughs".
(c) "Causes cough impulses without
narcotics."

(ii) Warnings. (a) "Do not take this
product if you have glaucoma or have
difficulty in urination due to an enlarged
prostate gland except under the advice
and supervision of a physician".
(b) "Do not give this product to
to children taking other drugs except
under the advice and supervision of a
physician".

(iii) Evaluation: Data to demonstrate
effectiveness will be required in accord-
ance with the guidelines set forth below
for testing antitussive drugs. (See part
III, paragraph C. below—Data Required
for Evaluation.)

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(11) Eddy, H. Halbach, "Codeine and Its
Alternates for Cough Relief," Benjamin
Curtis Publishing Co., Easton, Pa., p. 1090,
1975.
(12) "New and Nonofficial Remedies. Carbetapen-
tane Carboxylate," (for Evaluation.)
(13) "Caution: Do not give this product
without a prescription unless under the
advice and supervision of a physician.

(f) (Ref. 2). The Panel concludes that
the pharmaceutical industry should consult
with the Food and Drug Administra-
tion in the preparation of a routine test.
Otherwise, the Panel recom-
mends that each drug manufacturer
evaluate the dosage as labeled on the
manufacturer's marketed product(s).

(f) (Ref. 2). The Panel recommends
the Category I labeling for antitussive
active ingredients. (See part III, para-
graph B.I. above—Category I Labelling.)

(f) (Ref. 2). The Panel recommends
the Category I labeling for antitussive
active ingredients. (See part III, para-
graph B.I. above—Category I Labelling.)

(f) (Ref. 2). The Panel recommends
the Category I labeling for antitussive
active ingredients. (See part III, para-
graph B.I. above—Category I Labelling.)
that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).  

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients as stated in paragraph B.I. above—Category I Labeling.

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C. below—Data Required for Evaluation.)

References


(4) Ethylmorphine hydrochloride. The Panel concludes that ethylmorphine hydrochloride is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) Safety. Clinical experience has confirmed that ethylmorphine hydrochloride is safe in the dose range used as an antitussive.

There are few well-documented studies in animals and man defining the incidence of adverse reactions. Ethylmorphine is the ethyl ether of morphine, and its pharmacologic properties are similar to codeine, the methyl ether of morphine. Tolerance and physical dependence have been reported after prolonged use of ethylmorphine (Ref. 1). Other adverse reactions, such as constipation and respiratory depression, are similar to those of codeine. Topically, ethylmorphine is an irritant to mucous membranes and causes a burning inflammatory reaction with increased secretion of mucus (Ref. 2).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of ethylmorphine as an antitussive.

Animal studies employing induced cough showed ethylmorphine to have some antitussive activity (Refs. 3 and 4).

Since the early 1900’s, ethylmorphine has been used clinically at approximately the same dosage level as codeine. Because of its failure to demonstrate any advantage over codeine, it never attained the popularity of codeine as an antitussive (Ref. 5), and hence there are few studies demonstrating its use as an antitussive. Only one paper reported that ethylmorphine in a dose of 15 to 22.5 mg was as effective as to 60 mg of codeine in suppressing cough due to tuberculosis (Ref. 6). Unlike codeine, there are no objective clinical trials or well-controlled subjective studies in the literature.

Dosage range and pharmacologic activity, including adverse reactions and abuse potential, are similar to codeine. While ethylmorphine is regulated under the Federal Controlled Substances Act, it has not been tested at the Addiction Research Center, Lexington, KY because of its irregulant use (Ref. 5).

(3) Proposed dosage. Adult oral dosage is 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 mg every 4 to 6 hours not to exceed 22.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the labeling for Category I antitussive active ingredients. (See part III, paragraph B.I. above—Category I Labeling.) In addition, the Panel recommends the following for Evaluation: Data Required for Evaluation.

References


In eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) Safety. Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dose ranges used as an antitussive.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml, although recovery has occurred after doses of 29 and even 20 mg. Symptoms include edema of the lips and tongue, vomiting, lightheadedness, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing 1.3 percent eucalyptus oil was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, rash or blisters following the period of exposure (Ref. 3). A study of 10 subjects who received application of an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during the study (Ref. 4).

Vapors are also produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations of these vapors either due to sitting in closer proximity to the vaporizer or placing two to five times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Ref. 5).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 500 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. The incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil is also being tested for the treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently recently...
recalled from the market due to potential hazards of this substance (Ref. 13).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of eucalyptus volatile substances (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is a component of a number of currently marketed OTC topically applied preparations utilized as antitussives, e.g., ointments, steam inhalation, and lozenges. In a crossover study involving 18 subjects, the effects of a 1.3 percent eucalyptus oil in petrolatum ointment applied to the chests of the subjects, was compared to an ointment containing several volatile substances, including 1.3 percent eucalyptus oil, and to petrolatum in suppressing a citric acid aerosol induced cough. The combination ointment containing eucalyptus oil induced a significant decrease in cough counts at all challenge times from 0.5 hour to 2 hours averaging about 20 percent decrease at the 0.5 and 1 hour intervals and a reduction of about 10 to 20 percent reduction at these times, and the petrolatum induced no significant decrease in cough counts compared with base line (Ref. 15). Similar results with a combination ointment containing 1.3 percent eucalyptus oil were obtained in two additional induced cough studies conducted by the same investigator (Refs. 14 and 15).

A single-blind crossover cough counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest application of either the ointment containing several volatile substances an ointment containing several volatile oil's including 1.3 percent eucalyptus oil or a placebo (petrolatum base). Neither the ointment mixture of volatile substances nor the eucalyptus containing ointment produced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough count reduction compared to placebo was obtained following the afternoon application of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment but this was not statistically significant (Ref. 16).

A liquid mixture of volatile substances was evaluated on the subject by placing 1 tablespoonful per quart of water into an open container of boiling water. For topical use as a mouthwash 3 oz (20 mg/ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician. (See part 311.

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(4) Labeling. The Panel recommends: Category I labeling for eucalyptus oil as an active ingredient. (See part 311.

C. be-

(5) Evaluation. The Panel made the following recommendations:

(1) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(2) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)
PROPOSED RULES

(III) For topical use as a lozenge: Data
to demonstrate effectiveness will be re-
quired in accordance with the guidelines
described in Section H. Ingredients Index,
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CRD 71-37," Draft of unpublished data is
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CRD 71-37," Draft of unpublished data is
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CRD 71-37," Draft of unpublished data is
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tussive Cough Citric Acid Aerosol Technique,
CRD 71-37," Draft of unpublished data is
included in Volume 040298.
healthy subjects, 50 adults and 20 children ages 8 to 12, half dissolved a menthol containing lozenge and the other half a blank placebo. An average decrease in cough counts compared to placebo resulted when 2.8 percent menthol was included in the lozenges. A single-blind crossover cough-counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest applications of either the ointment mixture, containing 2.8 percent menthol, or petrolatum base. Neither the ointment mixture nor the petrolatum alone induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of the ointment containing the petrolatum base without the aromatics. In this instance, the therapy was discontinued (Ref. 40). A liquid mixture of volatile substances added to the water base of the medicated steam showed significantly lower cough counts than doses of medicated steam for the 4 hours the patients were exposed to vaporization and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with serious or even relatively proved adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations, either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the water base of the medicated steam was associated with irritating or toxic effects (Refs. 24 and 25). In two studies, 40 healthy subjects who were each given two canes of a volatile base lozenges, each lozenge containing 1.36 mg of menthol together with other volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70

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cough-standardized normal subjects were tested with each of two lozenge formulations, i.e., the active formulation and its placebo, both of which were artificially induced by the citric acid aerosol technique. Two studies involved lozenges in which menthol was the principal active ingredient and, consequently, reduction of the effectiveness of this mode of administering menthol to suppress cough. One of the studies involved 18 subjects using a lozenge containing 1.13 mg plus citric acid flavoring, produced greater cough reduction than the control lozenge although both the active and control lozenges in this study produced cough reductions at these time intervals (Ref. 49). The other study of 9 subjects, utilizing a lozenge containing 0.42 mg/ml menthol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 50).

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be repeated up to 3 times daily. (ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steaming vaporizer, boil or wash hands after 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medication (15 mg per dosage). May be repeated 3 times daily. (iii) For topical use as a lozenge 1.0 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour. (iv) For use as a mouthwash 0.42 mg/ml solution: Gargle with ½ oz (20 ml) twice daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labelling. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III, paragraph B.I. above—Category I Labelling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning: “For external use only. Do not take by mouth or place in nostrils.” (ii) For steam inhalation use: Warning: “For steam inhalation only. Do not take by mouth”.

(5) Evaluation. The Panel made the following recommendations: (i) For antitussive efficacy demonstrated effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C, below—Data Required for Evaluation.)

For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C, below—Data Required for Evaluation.)

For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C, below—Data Required for Evaluation.)

References...


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(23) Williams, H. J., Collection of unpublished data is included in OTC Volume 040298.


(32) Summary of Human Safety Data is Included in OTC Volume 040298.


(38) Larkin, V. P., “Vaposteam (commercial package, Intensive Use),” Draft of unpublished data is included in OTC Volume 040298.


(41) Packman, E. W., “VICTORS. Antitussive Screening: Citric Acid Aerosol Technique, CRD 71-17,” Draft of unpublished data is included in OTC Volume 040298.

(42) Packman, E. W., “VICTORS. Antitussive Screening: Citric Acid Aerosol Technique, CRD 71-17,” Draft of unpublished data is included in OTC Volume 040298.

(43) Proposed dosage. Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed a total of 80 mg in 24 hours. Children under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 80 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(44) Labeling. The Panel recommends that I label for antitussive active ingredients. (See part III paragraph B.1—above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to its central mechanism of action and its non-narcotic designation:

(1) Indications. (a) "Calms the cough control center and relieves coughing.

(2) "Non-narcotic cough suppressant for the temporary control of coughs." (c) "Coughs cough impulses without narcotics.

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III paragraph C. below—Data Required for Evaluation.) The Panel recommends that one experimentally induced cough study and one controlled study in patients with cough due to respiratory illness employing objective cough-counting techniques be performed in order to establish effectiveness as an antitussive.

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1. Thymol (topical/inhalation). The panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) Safety, Clinical experience has confirmed that thymol (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Thymol is an allyl derivative of phenol and has fungicidal, fungistatic and anesthetic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_50 of thymol in mice is 1500 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be burned to cause poisoning" (Ref. 4), thymol is presumably relatively nontoxic.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of thymol (topical/inhalant) as an antitussive. Experiments in anesthetized rabbits have indicated that thymol administered by "steam inhalation augmented the concentration of soluble mucus in the respiratory tract fluid" (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 1 gm/kg. The volume of thymol administered in the experiments was not stated. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol and propylene glycol appeared to suppress cirtic acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the antitussive activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9) and in steam inhalations (Ref. 10 and 11). Although significant antitussive activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder cough symptoms in individuals using the medicated mouthwash as compared to placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent preparation: To be rubbed on the throat, chest, and back as an "anti-thick layer. The area of application may be covered. Applications may be repeated up to 3 times daily.

(ii) For inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer. A 2 teaspoonfuls of solution per pint of water are added to a open container of boiling water. Breathe in vapor during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at 0.1 to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 0.5 mg: Allow lozenge to dissolve slowly in mouth or washbasin.

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III, paragraph C. below—Data Required for Evaluation.)

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12. OTC Volume 04028, m. Turpentine oil (spirits of turpentine) (topical/inhalant). The panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.
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(1) Safety. Clinical experience has confirmed that turpentine oil is safe when applied locally or used as an inhalant in the dosage ranges used as an antitussive. The Panel concludes that oil of turpentine is safe when applied externally or vaporized in a steam inhalant. (See Category I labeling.)

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of turpentine oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to a lack of properly controlled studies of the substance by itself.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be applied to the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbowl; or 2 teaspoonsful of solution per pint of water are added to an open container of boiling water. Breathe the steam during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III, paragraph C. above—Category I labeling.)

The Panel considers that certain words used in the context of claims for antitussives are statements which have no scientific meaning and therefore are misleading to the consumer. Additional data are required to support the following antitussive claims:

a. The term "soothing" in labeling such as "Calms coughing by soothing the irritated throat."

b. The term "throat soothing" in labeling such as "Throat soothing and recommended for coughs due to colds and dry, husky or tickling throats.

c. The term "smooth coat" in labeling such as "Produces a smooth coat that gives quick comfort to irritated throats and helps relieve coughs." The terms "demulcent action" and "soothes" in labeling such as "Demulcent action which gently soothes cough-Irritated throat membranes."

d. Duration of action unless there is acceptable documentation to verify this.

e. Terms relating to sleep such as "Quiets annoying cough and lets you sleep." An antitussive is capable of quieting annoying cough, but has not been demonstrated to be directly related to sleep.

f. The term "soothing" has not been scientifically demonstrated to have an antitussive effect. In fact, none of the antitussive ingredients reviewed by the Panel have any "soothing" properties since the Panel cannot determine what such a property would be. The same is true for the term "smooth". Again, the Panel is unaware of how the ingredients act to smooth an irritated throat or sooth membranes by a "demulcent" action.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. Principles in the design of an experimental protocol for testing antitussive drugs. a. General principles. The effectiveness of an antitussive agent is dependent on its ability to relieve the coughing of patients with a variety of disease conditions associated with coughing. Relief of coughing may occur with a reduction in the frequency or number of coughs, or with a decrease in the intensity of coughing. Because coughing is such a common symptom occurring in health as well as disease, adaptation readily occurs to the extent that many patients are unaware of the extent of their coughing, and hence any subjective evaluation is apt to be highly variable and with an unacceptable margin for error. Objective studies employing the actual recording of the cough are...

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quired to document a decrease in cough frequency and/or intensity.

b. Selection of patients. The study design will depend on whether the patients in the study have chronic lung disease, acute cough, or both. Because cough study in patients with chronic lung disease, a crossover design could be used in a small group of 10 to 20 patients whose underlying pulmonary disease is relatively stable so that daily fluctuations in the recorded cough counts permitted prior to drug administration are minimized. The smoking habit of the patients must be carefully documented and maintained at the same level throughout the clinical trial. No smoking would be permitted during the actual recording sessions. For a cough study in patients with acute upper respiratory infection, a larger number of patients, averaging between 50 and 100, would have to be studied because of the marked variation in cough from day to day and hour to hour in upper respiratory infection. The patients would have to be assigned in a randomized design to either the placebo or drug group. The duration of the type of study could be improved by matching the groups for age, sex, severity of cough, and smoking habit.

c. Methods of study. To establish efficacy as an antitussive, objective controlled studies employing cough-counting techniques are recommended. Two types of investigation are acceptable to the Panel. These are:

(1) A study may be done in a small group of healthy volunteers, approximately 10 to 20 in number, who are preferably nonsmokers. If smokers are included, their smoking habits must be well documented and remain at the same level during the entire course of the study. Any departure from smoking habits must be documented and made part of the evaluation of data. The data obtained in such a study including smokers and nonsmokers should be evaluated separately before combined. A challenge technique employing cough-producing stimuli is used to assess, cough frequency, dose, and time responses against the experimentally induced cough. This is performed under laboratory conditions with a double-blind or suitably blinded, crossover design in suitably trained individuals.

(2) A double-blind, controlled study may be done in patients with cough due to respiratory disease. The dose and formulation of the drug to be tested would be as recommended for OTC use. Coughs are recorded and counted for standardized periods before and after giving the drug or placebo so that adequate comparisons can be made concerning the onset and duration of activity from a single dose, as well as the effect of multiple doses. As a model for OTC drugs, however, the requirement for long periods of testing would be unnecessary since effective relief should be obtained early and, in most instances, after 1 or, at most, 2 days.

d. Interpretation of data. Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories. All of the required studies in man should employ objective cough-counting techniques for recording the cough reflex. In the evaluation of these drugs for which no sufficient evidence of antitussive effectiveness and for the assessment of drugs that have not been submitted for review by the Panel, the two required studies should consist of either the challenge study with experimentally induced cough plus a study with cough in respiratory disease, or, alternatively, two studies by different investigators in patients with respiratory disease with at least one of the two studies conducted under the advice and supervision of a member of the Panel. A significant reduction in cough when compared with placebo by acceptable statistical analysis of the data will permit reclassification of such drugs into Category I.

All data submitted to the Food and Drug Administration must present both favorable and unfavorable results.

e. Evaluation of safety. Tests for safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose- response to maximum therapeutic effectiveness.

IV. EXPECTORANTS

A. General Discussion

Expectorants are agents that are used to promote or facilitate the evacuation of secretions from the bronchial airways to provide for the temporary relief of cough due to minor throat and bronchial irritation as well as with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The secretions (sputum or phlegm), expectorated consist in part of respiratory tract fluids (RTF) together with a varying mixture of saliva and postnasal secretions.

In general, the mechanisms of action of the expectorants have been shown to be due to one or more of the following: the stimulation of reflexes from the stomach (the major action of certain drugs that are irritants to the gastrointestinal tract and act through their direct effect on the secretory cells lining the airway when administered by inhalation or if excreted by the respiratory tract); and stimulation of centers in the brain such as the vomiting center. By facilitating the evacuation of secretions from the bronchial airways, local irritants are removed. In addition, by increasing the amount of mucus that covers and protects the lining of the throat and the bronchial airway, it is claimed that a "lubricating" or "soothing" action is exerted which relieves irritated membranes in the respiratory passages. While these effects may indirectly serve to diminish the tendency to cough, the mechanism of this indirect action is quite different from that of an antitussive which is specifically designed to inhibit or suppress cough. Any claim relating to the amelioration of cough must be supported by the type of studies suggested above for evaluation of antitussives. (See part III, paragraph C. above—Data Required for Evaluation.) Expectorants would be expected to have their major usefulness in the irritative nonproductive cough as well as those coughs produced by excessive amounts of thick, sticky secretions.

As a group, the expectorant drugs have been widely used for many decades in the form of liquid preparations. By and large, in the dosages used for OTC administration, these drugs have had a good safety record. The few exceptions, where hypersensitivity reactions or cumulative toxicity represents a distinct hazard, have been discussed under the individual sections. While the expectorants have been traditionally used for their effect on aiding in the expectoration of phlegm (sputum) and thus relieving certain aspects of difficulty in breathing, there is little or no evidence to document this. In summary, the Panel concludes that while many of the expectorants on the market are generally safe, most lack evidence of efficacy and furthermore, all expectorants must be clearly identified on the labels of drug products as having a primary effect on respiratory secretions and not primarily as an antitussive.

B. Categorization of Data

1. Category I Conditions under Which Expectorant Ingredients are Generally Recognized as Safe and Effective and Are not Misbranded

Category I Active Ingredient

The panel was unable to classify a claimed expectorant active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for OTC expectorant active ingredients to be generally recognized as safe and effective and not misbranded:

Indications. (1) "Relieves irritated membranes of the respiratory tract, including the bronchial tubes;" (2) "Relieves the cough of irritative".

"Category I Active Ingredient"

The panel was unable to classify a claimed expectorant active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for OTC expectorant active ingredients to be generally recognized as safe and effective and not misbranded:

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"Category I Active Ingredient"

The panel was unable to classify a claimed expectorant active ingredient as generally recognized as safe and effective and not misbranded.
persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician.

2. Category II conditions under which expectorant ingredients are not generally recognized as safe and effective or as misbranded. The use of expectorants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from OTC products until scientific testing supports their use.

**Category II Active Ingredients**

The Panel has classified the following expectorant active ingredients as not generally recognized as safe and effective or as misbranded:

- Antimony potassium tartrate
- Chloroform
- Codlode: Calcium iodide anhydrous, Hydro-die acid syrup, Iodized lime, Potassium iodide
- Ipecac fluid extract
- Squill preparations: Squill, Squill extract
- Turpentine oil (spirits of turpentine) (oral)
- Ipecac fluid extract

**s. Antimony potassium tartrate.** The Panel concludes that antimony potassium tartrate is not safe for OTC use as an expectorant.

1. **Safety.** Antimony potassium tartrate is not safe in the dosage range used as an expectorant.

The toxic salts of antimony are potent inducers of vomiting; they act on centers in the brain as well as locally on the stomach walls. Because the antimony ingredient in this preparation tends to accumulate in the body and not to be excreted in a manner similar to arsenic, the danger of toxic reactions increases with repetitive or chronic use. These toxic reactions consist of marked irritation of the stomach and intestinal mucosa. Pain in joints and muscles are common, and the muscles of the heart may be depressed. Abdominal pain, rash and vascular collapse as well as a number of cases of hemolytic anemia, some fatal, have been reported (Ref. 1). Such toxic effects have been seen with the use of the trivalent compound at higher doses for the treatment of helminthic infections; but even in doses suitable for expectorant activity, antimony potassium tartrate is considered too toxic because of its cumulative properties to be used as an OTC product (Ref. 1).

2. **Effectiveness.** There is no evidence that antimony potassium tartrate is effective as an expectorant.

When administered in subacute doses, antimony potassium tartrate theoretically exerts expectorant activity through reflex stimulation of the salivary and bronchial glands (Ref. 2). There is, however, not one documented study in either animals or man demonstrating its effect on cough, sputum production or respiratory tract secretions (Ref. 3).

3. **Evaluation.** Because of its toxicity and tendency to accumulate in the body, the Panel is of the opinion that even subacute doses present risks which outweigh whatever benefit theoretically might occur since there is no evidence to support effectiveness.

**REFERENCES**

3. OTC Volume 640190.

**d. Chloroform.** The Panel concludes that chloroform is not effective for OTC use as an expectorant.

1. **Safety.** The Panel concludes that the question of safety is dependent on dosage and abuse potential.

In doses of 4 to 8 ml orally, chloroform has been known to produce a narcosis similar to that occurring when administered by inhalation but developing more slowly and of longer duration (Ref. 1). Although as little as a teaspoonful of chloroform by ingestion is approximately 30 ml (Ref. 2), although as little as a teaspoonful has produced serious illness. Symptoms of irritation due to chloroform ingestion are often delayed for 2 or more days (Ref. 3). The problem of abuse at a chloroform party has recently been reported (Ref. 4).

3. Three documents concerning the safety of chloroform were submitted to the Panel for review and appropriate action. These pertaining to the possible carcinogenicity of chloroform (Ref. 5 and 6) and the acute toxicity of chloroform in rats with an extrapolation to a suggested "maximum permissible limit" in humans (Ref. 7).

The first document was a review of a report by Harris on the implications of cancer causing substances in Mississippi River water (Ref. 5). A detailed analysis of the toxicological data, presented together with a review of the statistical methods and the animal studies, is reported in full in the minutes of the 17th meeting of the Panel, Appendix 9 (Ref. 6). The data indicate that there are serious inconsistencies in the report which makes the extrapolation of the data to possible risks of cancer from chloroform in drinking water unacceptable. Furthermore, the evidence of carcinogenicity in mice is conflicting and inconclusive and its extrapolation to another species, man, is open to serious question. Appendix 9 concludes that for the report pertaining to the possibility of chloroform being a carcinogen in drinking water there is no evidence to support the possibility of carcinogenic hazard in the recommended dosages. This view is supported by an ad hoc Study Group on "Assessment of Existing Risk from Organic in Drinking Water" by the Environmental Protection Agency (Ref. 7).

The second document (Ref. 7) attempts to establish some guidelines on permissible limits of solvent residues in chemicals. The authors list the obvious limitations of their study, i.e., the difficulty of extrapolating from rat to man; an acute single dose study does not provide an answer regarding the effect of chronic exposure; and the questionable use of arbitrary conversion factors that have no scientific basis. Their revised figure for the permissible limit for chloroform is 0.25 mg/ml. The Panel’s recommended concentration of 0.4 percent by volume is therefore well within the authors’ suggested permissible limit, the Panel concludes that chloroform be available only as a flavoring agent at a maximum concentration of 0.4 percent which represents 0.004 ml/ml or 0.02 ml/5 ml (teaspoon) of a product dosage. This is well within their revised permissible limit of 0.25 ml/60 kg, of body weight.

The third document is a preliminary report from the National Cancer Institute entitled, "Report on Carcinogenesis Bioassay of Chloroform" dated February 1978 (Ref. 6). The protocol consisted of a total of 460 rats and mice with suitable control animals receiving the intraperitoneal injection of chloroform orally for a total of 546 days. The treated animals were divided into low and high dose groups.

Five rats in the study showed a decreased survival rate which appeared dose related. Clinical evidence of toxicity appeared during the first 10 weeks but became more apparent during the second year of the study. The control group also showed these signs by the 70th week. Transient palpable nodules were noted in both test and control rats by the end of the second year. The incidence of "all tumors" in both treated and control rats did not differ. Significant differences from control groups occurred with kidney tumors in male rats which appeared dose related and thyroid tumors in the female rats but the thyroid tumors were not considered relevant to the study because of the known incidence of thyroid tumors in the strain of rat. Neoplastic nodules of the liver occurred with equal frequency in test and control groups and there was a slightly greater frequency in the chloroform-treated rats.

For mice, results of the study showed that there were no significant differences in survival rate between the controls and treated mice except for the high dose female group. Beginning after 42 weeks of treatment, the chloroform-treated mice began to exhibit a definite, significant incidence of abdominal distention. The incidence of "all tumors" in the treated groups was significantly higher, and this was solely due to the presence of hepatocellular cancer.

The conclusions to be drawn from this study are that orally administered chloroform can produce hepatic neoplasms in this strain of rats when administered at these levels and for a prolonged period of time. There was a less striking correlation of kidney tumors with chloroform ingestion in the rat species. But the lack of any increase in neoplastic tumors in the rats or kidney tumors...
in the mice is attributed by the authors as illustrating "marked differences in organ specificity and sensitivity." The Panel questions whether this then can be extrapolated to other species such as dog or man.

The Panel has considered the dosage of chloroform administered in the study. The average 400-gm rat received 36 to 80 mg/day for 546 days or a total of 19,656 to 45,650 gm. The average 80-gm mouse received 3.2 to 12.0 mg/day for 546 days or a total of 2.184 to 7,644 gm. In terms of an average 60-kg human, the equivalent doses would be 5.4 to 12.0 gm/day or a total of 2,984.4 to 6,552.4 gm for 546 days. If the mouse dosage is extrapolated, the human dose would be 8.0 to 28.0 gm/day or a total of 4,338 to 15,128 gm. The Panel finds that the use of chloroform as a flavoring agent at a maximum allowable concentration of 0.4 percent or 0.4 gm/100 ml would require the consumption of 1.35 to 7 liters/day for a total of 737.1 to 8,322 liters in 546 days. If the usual cough mixture is dispensed in a 120 ml bottle, this would represent the consumption of 31,850 bottles in a 2-year period. The Panel questions how many other chemicals, flavoring agents, etc. would be toxic or even carcinogenic at these levels.

In the final analysis, the Panel is unable to determine on the available evidence the lack of safety of chloroform in man at the 0.4 percent concentration proposed for use as a flavoring agent. Obviously, there is a dose-response relationship with respect to toxicity and the potential for abuse exists just as with alcohol.

(2) Effectiveness. There is no evidence that chloroform is effective as an expectorant that it ameliorates cough.

There is no documentation of the expectorant activity of chloroform. One report (Ref. 9) states that it is "probably harmless as well as useless in the dosages used." The U.S. Dispensatory reports that chloroform has been added to cough mixtures as a respiratory sedative, but its action is too fleeting to be of any chronic administration. The effective dose is 900 mg daily in divided doses (Refs. 2 and 3). Leonard (Ref. 4) estimates the optimal dose at 23 to 35 mg/kg daily in divided doses. At these doses, there is a high incidence of toxic effects varying in seriousness from mild lodism which may simulate the symptoms of the "common cold," some individuals, though not frequently, are highly sensitive to iodides and will react to the first few doses with serious consequences (Ref. 1). Clinical experience with iodides has been more in the treatment of chronic diseases, such as bronchial asthma, chronic bronchitis, bronchiectasis and emphysema; therefore, this information is not directly applicable to this chronic administration. The effective dose is 500 mg daily in divided doses (Refs. 2 and 3). Leonard (Ref. 4) estimated the toxic dose at 23 to 35 mg/kg daily. At these doses, there is a high incidence of toxic effects varying in seriousness from mild lodism to generalized pulmonary congestive heart failure, emphysema, and various types of dermatoses. Because of the high incidence of untoward effects and the potential for toxicity, iodides should be used only under the advice and supervision of a physician.

(3) Effectiveness. Iodides may be effective as an expectorant when given in adequate doses in some chronic respiratory disease. There is no evidence that they are efficacious in acute upper respiratory infections. Animal studies have demonstrated the presence of iodides in the respiratory tract fluid (RTF) and an increase in the amount of RTF or a decrease in its viscosity. It has been suggested that this change in viscosity results from iodides reported by Galina, Avnet and Eisenhawen (Ref. 8). Continued heavy use in children and adults may produce gouty or hypothyroidism (Refs. 9 and 10). The Medical Letter (Ref. 11) discusses the hazards of long-term exposure to iodides as the most frequent cause. The blood levels needed to induce gout or hypothyroidism are not yet established. Fuller et al. (Ref. 2), in a 3-year double-blind study of 52 children with chronic asthma, demonstrated a statistically significant improvement in the children receiving potassium iodide 300 mg 3 times daily. The population receiving iodide had a greater improvement in FEV1 variability in the response of the individuals in the study, and there is no an-
sider to why. It may be due to some other property than that of its expectorant property.

While the iodides are possibly expectorants, there are insufficient studies to confirm this. This would suggest the need for more complete studies and better techniques for evaluation of the action of iodides.

3. Evaluation. The Panel concludes that iodides are not safe for OTC use. Because of the number of diseases which concomitantly their use and because of the potential for toxicity and untoward effects, iodides should be used only under the advice and supervision of a physician.

REFERENCES
(8) Wilkins, E. K., "The Con-}
renal irritation, bloody stools and hyperemia of all abdominal organs. Continued oral use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an expectorant, the Panel concludes that turpentine oil should not be available for oral OTC use as an expectorant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an expectorant. See part IV. paragraph B.3.n. below.

Effects. Oil of turpentine is irritating and its chief suggested uses are as a rubefacient (topical/inhalant).

The Panel concludes that turpentine oil is safe for oral use as an expectorant. The Panel has previously concluded that ammonium chloride is safe for oral use as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that no objective evaluations have been reported. Partially controlled subjective studies (Ref. 7) showed no significant change in either sputum volume or viscosity. Several investigators (Refs. 8 through 10) felt that sputum was more fluid and easier to raise when given at doses of 0.3 gm every 2 hours, and Saub, Hollinger and Foncher (Ref. 11) reported a decrease in viscosity and pH differential (neutrity) in patients with damaged bronchial tubes and infection.

Proposed dosage. Adult oral dosage is 300 mg every 2 to 4 hours. Children 6 to under 12 years oral dosage is 150 mg every 2 to 4 hours. Children 2 to under 6 years oral dosage is 75 mg every 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1 above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warnings. (1) "Caution: This product must be taken with adequate amounts (1/2 to 1 glass) of fluids with each dose."

(2) "Do not take this product if you have heart trouble or chronic kidney or lung disease except under the advice and supervision of a physician."
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(5) Evaluation. Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C below—Data Required for Evaluation.)

REFERENCES


b. Beechwood creosote. The Panel concludes that beechwood creosote is safe in the dosage range used as an expectorant but there are definite data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that beechwood creosote is the usual dosages contained in lozenges or cough mixtures for expectorant activity is safe.

Creosote is a distillate of wood tar and has a smokey odor and a pungent taste. Dosages in excess of 4 gm 2 times daily produces gallbladder, dizziness, pain in vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is usually well-tolerated (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of beechwood creosote as an expectorant. No controlled or partially controlled studies were submitted to the Panel documenting its effectiveness as an expectorant. Only one reference (Ref. 4) confirmed that decreases in respiratory tract fluid (RTF) in animals given high dosages but the authors expressed doubt as to the applicability of these data to humans and to the standard body of evidence at this time. An average dose of beechwood creosote is 250 mg 3 to 4 times a day. In the two submissions to the Panel listing creosote, the dosage range was 75 to 100 mg/kg every 3 hours (Ref. 5). This gives a 20-fold difference in dosage (3.29 mg/lozenge, 5 doses daily) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) Proposed dosage. Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1,500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends that the Category I labeling for expectorant active ingredients. (See part IV, paragraph B.1. above—for Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

REFERENCES


(5) OTC 74-04225.

c. Benzois preparations (compound benzois tincture, tincture of benzois (inhalant). The Panel concludes that tincture of benzois and compound benzois tincture are safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that benzois tincture and compound benzois tincture are safe in the dosage ranges used in boiling water or other species of the Section An

thostyris of the genus Styraex, known in commerce as Slam benzois (San. Styraex) (Ref. 1). Benzois is used in preparing official preparations, e.g., compound benzois tincture, United States Pharmacopoeia XIX (Ref. 1) and benzois tincture, National Formulary XI (Ref. 2).

Benzois contains 74% to 80% percent alcohol and is prepared by a maceration process incorporating benzois, aloes, storax and tula balsam using alcohol as a menstruum. The benzois tincture contains 74 to 80 percent alcohol and is also prepared by macerating benzois, the final product being a 20 percent solution of benzois (Ref. 2). These preparations are used topically as a protectant and antiseptic and by steam inhalation as an expectorant (Refs. 3 and 4).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of benzois and compound benzois tincture as an expectorant.

Although compound benzois tincture and benzois tincture have been advocated and used for generations as a component of steam inhalations to promote an expectorant action, no studies demonstrating this effect have been found in the literature or OTC submissions.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years of age is as follows: Add 1 teaspoonful of compound benzois tincture or benzois tincture to a pint of water in a hot steam vaporizer, bowl or washbasin. Breathe in vapors during the period of mediated steam generation. May be repeated 3 times daily. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends that the Category I labeling for expectorant active ingredients. (See part IV, paragraph B.1. above—for Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warnings: "For use by steam inhalation only. Do not take by mouth."

(5) Evaluation. Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

REFERENCES


FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
d. Camphor (topical/inhalant). The Panel concluded that camphor is safe in the dosage ranges used when applied topically or as an inhalant but that there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant. (1) Safety. Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are due to the penetration of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.78 gm contained in a teaspoonful of liquid camphor or camphorated oil that contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an expectorant. However, the Panel believes that certain due to lack of properly controlled studies of the substance by itself. A standard text indicates that camphor may have a slight expectorant action (Ref. 1). Well-controlled specific studies to document this effect have not been found in the literature.

(3) Proposed dosage. Dosage for adults and children 12 years and under 13 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. Application may be repeated 3 times daily. However, clothing should be left loose about the throat and chest to help the vapor rise to the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water, usually in a tea or coffee pot, or steamer, or washbowl; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in the vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 0.15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice of supervision of a physician.

(4) Labeling. The Panel recommends the following specific labeling: (i) For topical ointment use: Warning: "Do not take by mouth."

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth."

(5) Evaluation. The Panel made the following recommendations: (i) Topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C below—Data Required for Evaluation.)

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References


e. Eucalyptol/eucalyptus oil (topical/inhalant). The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 ml. Symptoms include epiglottic burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in whom an ointment containing several volatile substances, including eucalyptol, was applied for 88 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, rash, or burning during the period of exposure (Ref. 3). A study of ten subjects who received application of an ointment containing several volatile substances including eucalyptol oil for 1.5 percent to their thorax, neck and chest for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase. One infant and children with respiratory infections who received an ointment containing a mixture of volatile oils, including eucalyptus oil, did not exhibit any adverse effect from inhaled vapors by that route of administration in the rate of clearing of laryngeal edema (Ref. 3). In contrast, symptoms in-duced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation of the generated vapor on adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting too close to the vaporizer or placing 2 to 6 times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenge containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 0.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. Incidence of gastrointestinal symptoms did not differ from control either (Refs. 6 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate snorting abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently recalled from the market because of potential hazards of this substance (Ref. 13).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.
of direct stimulation of bronchial secretory cells following inhalation (Ref. 14). In one study, eucalyptus oil was administered via the vaporizer, bowl or washbasin; or 2 teaspoons of solution per quart of water is added to the water in a hot steam vaporizer. Breath in vapors during the period of medicated steam generation. (2) For topical use as a lozenges 0.2 to 1.50 mg: Allow lozenges to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour.

(3) Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.7 percent ointment preparation: To be rubbed on the chest, throat, and mouth for a thick layer. The area of application may be covered. However, clothing should be left loose over the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoons of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenges 0.2 to 1.5 mg: Allow lozenges to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour.

For children under 2 years, there is no recommendation of the use of eucalyptus except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category II labeling for expectorant drugs. Security Screening (See part II. l. h. above—Category I Labeling). In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning: "External use only. Do not take by mouth or place in nostrils". (ii) For steam inhalation use: Warning: "For Evaluation only. Do not take by mouth".

(5) Evaluation. The Panel made the following recommendations: (1) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For topical use as a lozenges: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(iii) From this observation the authors concluded that eucalyptol does not act directly upon the secretory cells of the respiratory tract (Ref. 14).

Eucalyptol was shown to be an expectorant in rats, guinea pigs, rabbits, cats, and dogs. The effect was not induced by section of the afferent gastric nerves. From this observation the authors concluded that eucalyptol does not act by a reflex mechanism in the stomat. A small study, this group administered eucalyptol by stomach tube to anesthetized animals. Eucalyptol was shown to be an expectorant in rats, guinea pigs, rabbits, cats, and dogs. The effect was not induced by section of the afferent gastric nerves.
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although trends could be detected at 7 days. The report by Thomson, Pavia and McNicol (Ref. 25) showing a significantly faster clearance of inhaled radioactive particles over the first 4 hours with glyceryl guaiacolate than with single doses of 200 mg as compared to placebo in bronchitic patients in a double-blind crossover study is of special interest both in the evaluation of secretory activity as an objective type of assessment for expectorant drugs. This is a new approach to the study of expectorants and is objective in design. If results can be confirmed, it may represent a "breakthrough" in methodology.

If glyceryl guaiacolate requires 7 to 10 days to begin to demonstrate a significant expectorant effect, it is obviously not suited for OTC use where rapid relief of symptoms in a self-limited illness of relatively short duration is desired. It should be emphasized that a study by Thomson, Pavia and McNicol (Ref. 25) suggesting drug activity is a single study that has not been confirmed by any other investigator. Hirsch et al. (Ref. 2) published another report employing another objective controlled method of study, were unable to demonstrate effectiveness. It would appear that the contradictory results of these two studies conflict with each other in a manner of speaking.

A recent subjective double-blind study was submitted in which there were 121 patients in a placebo group and 118 who received 200 mg every 6 hours for a period of 72 hours (Ref. 26). Statistical analysis of the data was reported as showing a significant reduction in cough frequency and intensity in the patients on glyceryl guaiacolate. However, this conclusion by a subjective method of evaluation is unacceptable as a claim for suppression of cough frequency or intensity in keeping with the Panel's statement that effectiveness of a drug with respect to antitussive activity must be assessed by objective methods. Such a subjective method as described is said to be unable to demonstrate effectiveness. (See part IV, paragraph B.1 above—Category I Lobbing.)

Evaluation of effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. Effectiveness to be established by only one additional controlled study which in view of the difficulty in obtaining objective criteria for such evaluations, could be a well-designed subjective study. (See part IV, paragraph C. below—Data Required for Evaluation.)

In addition, this study reported that glyceryl guaiacolate administration was associated with a reduction of a significantly thinner sputum and was effective in increasing sputum volume and facilitating the raising of secretions in patients with expectorant cough. In examining the data, it was noted that one investigator in this multidisciplinary study submitted two separate studies with a total of 76 subjects which accounted for 45% of the total subject population. Another investigator presented data that showed no significant difference from placebo and a third investigator showed a significant trend in favor of glyceryl guaiacolate. Because of the conflicting results of the different investigators on this study and the likelihood that the data from the single investigator biasing the results would bias the results of the study when all the information is pooled, serious questions are raised as to the validity of the study. Retrospective analysis of the data with respect to smoking showed that there was no bias introduced by the incidence of smoking of the subjects (Ref. 27).

There are a number of controlled, objective studies with combinations of theophylline and glyceryl guaiacolate in reversible airway obstruction studies but these were not relevant to its expectorant activity.

There is considerable dispute as to the effective dosage. From the more recent reports in the literature it would appear to be 2 to 4 times higher than the customary dose of 100 mg.

(3) Proposed dosage. Adult oral dosage is 500 to 600 mg every 4 hours not to exceed 2400 mg in 24 hours. Children 2 to under 6 years of age 1 to 2 years old not to exceed 600 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

Hirsch, Viernes and Kory (Ref. 21), employing another objective controlled method of study, were unable to demonstrate effectiveness. It would appear that the contradictory results of these two studies conflict with each other in a manner of speaking.

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Hirsch, Viernes and Kory (Ref. 21), employing another objective controlled method of study, were unable to demonstrate effectiveness. It would appear that the contradictory results of these two studies conflict with each other in a manner of speaking.
when given orally, there is no information on the absorption of small doses from the gastrointestinal tract, or on the cumulative effects of repeated administration. In view of possible cumulative effects from oral administration, the Panel recommends a 1-week time limit of use for any only exception except when given under the advice and supervision of a physician.

Based on the long history of use and on the available data, the Panel concludes that when given in small doses as proposed below, ipecac syrup is safe for OTC use.

(3) Effectiveness. In large doses, ipecac is an emetic. However, in the subcutaneous dosages used as an expectorant, its effectiveness is questionable. There are no acceptable clinical studies to substantiate its use as an expectorant.

Practically all the work with ipecac was done more than 2 decades ago. Animal studies using varying preparations of ipecac indicate that this drug may increase the flow of respiratory tract fluid (Refs. 3 through 7). Several controlled studies in human subjects with chronic cough did not demonstrate that ipecac was effective as an expectorant when applied topically or as an inhalant but are insufficient to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Menthol is the chief constituent of peppermint oil. It contains properties. In one study, a 20 percent solution of peppermint oil, administered at recommended doses was not associated with irritating or toxic effects, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of peppermint oil, administered to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucous membranes irritates whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 233 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal formation, or excoriation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypertrophic redness and contact dermatitis (Ref. 4). A study of 10 subjects who received an application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for two weeks, then 1 week off, followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). One study suggests that the administration of menthol inhalant to adults increases with increased duration of use. This survey revealed an incidence of less than 1 percent menthol psychosis in 542 patients using a mentholated ointment for less than 10 years, whereas an incidence of 3.4 percent hyperpermeability was seen in 411 patients using this type of preparation for longer than 10 years (Ref. 9).

In infants and small children, nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nose of adults has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile substances including 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors that occurred in adults or children (Ref. 22). A controlled study of laryngeal inflammation. In this study 55 children, 23 under 2 years of age, with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children, 20 under 2 years of age, received standard therapy plus the mentholated ointment applied to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.60 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several times the recommended exposure concentrations either due to sitting in close proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer was not associated with irritative or toxic effects (Refs. 24 and 25).

In two studies, 40 healthy subjects asked to dissolve two candy-base lozenges containing 26 mg of menthol together with volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of healthy subjects, 60 adults and 30 children ages 8 to 12, only 26 percent experienced a menthol-eucalyptus lozenge containing

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9.63 mg menthol and 5.55 mg eucalyptus oil every 4 to 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on day 1 and day 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complications were reported (Ref. 28). A study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29). An aerosolized dosage form of volatile substances containing 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behavioral responses or airway tissues abnormality upon autopsy examination (Ref. 30). Sensitization was not observed upon patch testing with 1 percent menthol ointment containing 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8-hour period for 14 consecutive days in a mouse. Eye irritation: The only pharmaceutically toxic effect observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deliberate snuffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial pharmaceutical product, a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhaled) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself. The local anesthetic effect of menthol vapor has been the justification for including menthol in topically administered ointments, preparations, and solutions for the relief of cough. In a crossover study involving 16 subjects the effects of a 2.8 percent mentholated petrolatum ointment applied to the chest of the subject was compared to an ointment containing several volatile substances including 2.8 percent menthol, and to petrolatum in suppressing a citric acid aerosol-induced cough. In a separate study containing menthol induced a significant decrease in cough counts at all challenge times from 1/2 hour through 2 hours, averaging about 9 percent decrease at the 1/2 and 1 hour intervals, whereas the single ingredient menthol ointment yielded a significant decrease in cough counts just at the 1/2 and 1 hour intervals, averaging about 10 percent decrease at both time intervals. The petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 34). Similar results with the combination ointment containing 2.8 percent menthol were obtained in two additional induced-cough studies conducted by the same investigator (Ref. 35 and 36).

A single-blind crossover cough-counting study of 27 patients exhibiting a pronounced increase in chest secretions was conducted twice daily chest applications of either the ointment containing volatile substances including 2.8 percent menthol, an ointment containing eucalyptus oil, or petrolatum base. Neither the ointment mixture nor the eucalyptus oil ointment induced a significant decrease in cough counts compared with placebo after this application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 20 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment, but this was not statistically significant (Ref. 37).

A liquid mixture of volatile substances added to the water of a hot steam vaporizer and administered via inhalation contained menthol 3.66 percent, camphor 7 percent, eucalyptol 7 percent, and cineole 1 percent, and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid to water at 1 tablespoon of water, to steam alone in suppressing coughs artificially induced by the citric acid aerosol technique. In each case both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration: In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subject (Ref. 37, 38, and 39). Subjective evaluation studies of adults and infants having cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of the volatile substances in steam, 1 tablespoon per quart of water, and of steam alone. A placebo control of medicated steam was studied for its ability to suppress citric acid threshold. An 1 mg and eucalyptol 0.25 mg, citrated citric acid thresholds of 120 + 7.9 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 39). A crossover study of 10 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10- to 40-minute challenge periods, reaching a peak of 33 percent reduction at the 10- and 20-minute intervals whereas the control lozenge produced a significant reduction of 10 to 15 percent maximum at only the 10-minute challenge (Ref. 40). In another study of 10 subjects receiving doses of menthol 1.5 mg and eucalyptol 0.35 mg, citrated citric acid thresholds of 120 + 7.9 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 37). A study of 20 subjects utilizing a formulation containing menthol, eucalyptol, camphor, thymol, and tol balsam present in subjects utilizing in the preceding study (Ref. 49). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol, and tolu balsam producing significant cough reductions at the 10- to 40-minute challenge period, reaching a peak of 33 percent reduction at the 10- and 20-minute intervals whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10- and 20-minute challenge periods only (Ref. 40). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptol, camphor, thymol, and tolu balsam in subjects utilized in the preceding study (Ref. 49).

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a lozenge preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoon of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoons of solution per pint of water are added to the container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 1.0 to 12 mg: Allow lozenge to dissolve
slowly in mouth. May be repeated every 1/2 to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for expectorant-active ingredients. (See part IV, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning: "For external use only. Do not take by mouth or place in nostrils.

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth.

(5) Evaluation. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

REFERENCES


(7) Kligman, A. M., "Trunk Rub Study (V 33-34)," Draft of unpublished data is included in OTC Volume 040298.


(11) Carter, V. H., "VAPOSTEAM. Broad Clinical-Efficacy Study. The active ingredient is pine tar. Dosage is not controlled. The above preparations are safe in the dosage range used as expectorants but effectiveness at the dosage range has not been established. The following specific labeling: (i) For topical ointment use: Warning: "For external use only. Do not take by mouth or place in nostrils.

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth.


(17) Kligman, A. M., "Trunk Rub Study (V 33-34)," Draft of unpublished data is included in OTC Volume 040298.


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liquid. It has a turpentine-like odor and a sharp taste of organic decomposition. It has been used empirically, for many decades, in the treatment of diseases of the skin, being slightly irritating, antiseptic, and with local anesthetic properties. The panel is unaware of any studies to evaluate the safety of pine tar. It is probably safe in the recommended doses since it has been used for decades without any recorded reports of adverse effects.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of pine tar preparations as expectorants. The use of pine tar preparations as expectorants appears to be based solely on tradition. There is no evidence that they are effective as an expectorant when taken orally.

(3) Proposcd dosage. Adult oral dosage is 1.6 mg every 2 to 4 hours. Children 2 to under 12 years oral dosage is 0.8 to 1.0 mg every 2 to 4 hours. Children 2 to under 6 years oral dosage is 0.4 to 0.5 mg every 2 to 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labelling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labelling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

REFERENCES


J. Potassium guaiacolsulfonate. The Panel concludes that potassium guaiacolsulfonate dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience over more than a half a century has confirmed that sodium citrate is safe in the dosage ranges used as an expectorant. It is mildly diuretic and, in larger doses, may be laxative. Gastric irritation can be produced in the absence of undiluted drug formulation is sparce, and there is no documentation of adverse reactions.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of potassium guaiacolsulfonate as an expectorant. While subjective studies would indicate that it is ineffective as an expectorant (Refs. 1 and 2), potassium guaiacolsulfonate has been used empirically for many decades as an expectorant mixture. Connell, et al. (Ref. 3) showed no change in water content of the respiratory tract of rats. Two papers cited that potassium guaiacolsulfonate is not metabolized to guaiacol (Refs. 1 and 2).

(3) Proposed dosage. Adult oral dosage is 1.6 mg every 2 to 4 hours taken well diluted with at least 1/2 glass of water or fruit juice (Ref. 3). Children 0 to under 12 years oral dosage is 0.8 to 1.0 mg every 2 to 4 hours diluted as above with water or fruit juice. Children 2 to under 6 years oral dosage is 0.4 to 0.5 mg every 2 to 4 hours diluted as above. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labelling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labelling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

REFERENCES


1. Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir). The Panel concludes that terpin hydrate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that terpin hydrate is safe in the dosage ranges used as an expectorant. A few papers noted gastrointestinal distress from dosages of 340 to 689 mg/24 hours, with nausea and vomiting (Refs. 1 and 2). Elixir terpin hydrate has a high alcoholic content of approximately 42 percent by volume. (Ref. 3). The Panel recognizes the potential for such abuse as stated in a previous section of this document. (See part IV. paragraph A. above—Drug Misuse and Abuse.) Based on the available data and its long history of use, the Panel concludes that terpin hydrate is safe for OTC use in the dosages discussed above. However, which should be subject to label abuse. (Ref. 3). The Panel recommends that the label for terpin hydrate not be used in children younger than 12 years.

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(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of terpin hydrate as an expectorant. The majority of papers in the literature question the effectiveness of terpin hydrate and indicate that it is probably harmless and useless (Refs. 2 through 5). Two papers indicate that at a dose of 300 mg 4 times daily, it had a "loosening effect," but these were subjective evaluations (Refs. 6 and 7). The Panel concludes that the information available is not sufficient to determine that terpin hydrate is effective as an expectorant.

(3) Proposed dosage. Adult oral dosage is 300 mg every 4 hours not to exceed 1200 mg in 24 hours. The elixir should not be given to children under 12 years of age but terpin hydrate by itself or in a nonalcoholic mixture can be used. Children 6 to under 12 years oral dosage is 100 mg every 4 hours not to exceed 600 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 mg every 4 hours not to exceed 300 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warnings. (1) "May produce nausea and vomiting".

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

(1) Safety. Clinical experience has confirmed that terpene preparations are safe in the dosage ranges used as expectorants. Tolou balsam can be considered safe in the dosages used for expectorant activity when administered orally or by inhalation.

There is no documentation as to toxicity at the dose levels in general usage in man. One report (Ref. 1) states that "large doses, 10,000 times set forth below, when given by inhalation produced an acute inflammation of the tracheal lining in rabbits." (2) Effectiveness. There are no well-controlled studies documenting the effectiveness of tolou preparations as expectorants. There is no evidence that tolou balsam possesses expectorant activity.

Several reports by Boyd and his co-workers (Refs. 2 through 4) are conflicting and consist for the most part of statements rather than data from studies, i.e., "Syrup of Tolou did have an expectorant action." Certain volatile oils (Frass's balsam) stimulate the output of respiratory tract fluids (RTF) or bronchial secretions (Ref. 3). In another paper (Ref. 4), the author states that inhalation by animals of volatile doses of certain volatile oils (Frass's balsam) has no effect upon respiratory tract fluids. A standard text states that tolou balsam syrup is "useful as a vehicle for expectorant drugs but has no specific virtue for this purpose" (Ref. 5).

The Panel takes cognizance of the fact that tolou balsam has been used for many decades as an ingredient in steam inhalations and in oral expectorant mixtures but concludes that there are insufficient data to determine the effectiveness of tolou balsam as an expectorant.

(3) Proposed dosage. Adult oral dosage is 50 mg every 2 or 3 hours. Children 6 to under 12 years oral dosage is 25 mg every 2 to 3 hours. Children 2 to under 6 years oral dosage is 12.5 mg every 2 to 3 hours. For children under 2 years, there is no recommended dose except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category II labeling for expectorant active ingredients. (See part IV, paragraph B.1. above—Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

(1) Safety. Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dose ranges used as an expectorant. The Panel concludes that turpentine oil is safe when applied externally or vaporized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an expectorant. (See part IV, paragraph B.2.1. above—Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of phenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found no evidence of a vaporized concentration of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary artery, resistance or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold," no side effects that were drug related were observed when a medicated ointment was administered (Refs. 0 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years, with approximately two complaints per million packages purchased (Ref. 14).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of turpentine oil as an expectorant. Turpentine oil is usually vaporized in boiling water as a steam inhalant due to a lack of objective measurement studies of the substance by itself.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (1) For topical use as a 5.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thin layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help...
The vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(1) For steam inhalation use a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(2) Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (1) For topical ointment use: Warning: "For external use only. Do not take by mouth or place in mouth expectorant.

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) Evaluation. The Panel made the following recommendations: (1) For topical ointment, use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients' respiratory disease in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.) (1) For steam inhalation, use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV, paragraph C. below—Data Required for Evaluation.)

REFERENCES


2. Memo to G. P. Hoffmeyer from A. R. Blanchette, "Vaporub—Levels of Aromatics from a Vaporizer," is included in OTC Volume 04298.


5. Watanabe, T. and D. M. Aylward, "Cardiopulmonary Effects of Turpentine in Mice," direct unpublished data is included in OTC Volume 04298.


14. OTC Volume 04297.

CATEGORY III LABELING

The Panel concludes that substantiation by additional data is required before statements regarding duration of action, e.g., "all day", "all night", "for hours" will be acceptable. Such statements must specify in the labeling the number of hours of relief claimed. The statements must be verified by appropriate documentation.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocol commencement for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology for data required. The data required is as follows:

I. Principles in the design of an experimental protocol for testing expectorant drugs. a. General principles. The effectiveness of an expectorant preparation is based on its ability to facilitate the removal of sputum from the respiratory passages and thus clear the airway of retained secretions. By aiding in the evacuation of these secretions and through a soothing effect on irritated mucous membranes, it will indirectly care the act of coughing. While the ease in raising secretions may seem simple to measure and assess, there are at present no suitable objective methods for evaluating this. Difficulty stems, in part, from a lack of basic knowledge concerning the biochemical and physiochemical nature of respiratory tract secretion in various respiratory diseases, as well as the chances produced by expectorant drugs, and the lack of evidence as to which property of sputum correlates best with ease of expectoration. Because of this, the subjective evaluation of the patient must be relied upon the assessment of the drug's expectorant activity.

b. Selection of patients. Based upon the method of study to be used, two types of patients may be selected. One patient type who would be chosen for a crossover study would include subjects with chronic cough due to chronic pulmonary disease such as chronic bronchitis, pulmonary emphysema, inactive pulmonary tuberculosis, or chronic atelectasis. Selection is relatively stable with no evidence of intercurrent infection that would affect cough or character of the sputum. A second patient type could include subjects with an acute upper respiratory infection such as an acute bronchitis or tracheobronchitis, in which a dry nonproductive cough is a prominent feature. Because the production of sputum may be influenced by other systems, such as the circulation, patients with congestive heart failure or significant renal or hepatic disease must be excluded. Furthermore, every effort must be made to minimize the risk in crossover trials of contaminants and activity, and drugs must be prohibited that may affect sputum, such as the anticholinergics and antiangiotensins. While members of the panel believe that such trials should be conducted in patients whose smoking habits of patients must be carefully documented and maintained at the same level throughout the clinical trials. No coughing would be permitted during the collection of secretions. While impractical to control, the effect of environmental factors such as temperature, humidity, and degree of air pollution should be recognized.

c. Methods of study (1) Double-blind crossover design in patients with chronic lung disease. A suitable period for baseline studies must be performed prior to the administration of the test drugs. During this period, the following subjective indices will be noted: Ease of expectoration; character of the cough (whether productive or not); frequency of coughing; and breathing comfort, i.e., heavy, noisy, rattling, etc. Additional help in evaluating effectiveness may be provided by some objective indices such as: The time required to expectorate sputum over a given time (12 to 24 hours); the character and color of the sputum raised; and some measure of its flow properties, such as viscosity or consistency. If a cough suppression claim is to be substantiated, an objective cough-counting study must be done as discussed above under antitussives. (See part III, paragraph C. above—Data Required for Evaluation.) Following baseline studies, similar observations are obtained during the administration of the drug and placebo which must be indistinguishable from each other, randomized, and provided at the same dose and length time recommended for OTC use. This type of study would require approximately 3 weeks, 1 week on each preparation and 1 week for the baseline data.

(2) A randomized double-blind design in patients with acute upper respiratory infections. Groups of patients would receive either a placebo or the drug under study in a similar dose and time interval as recommended for OTC use over a period of 3 to 5 days. Similar observations, as discussed above, would be obtained where possible to evaluate effectiveness, but no prior baseline period would be obtainable with this model and most of the data would be limited to the subjective indices. Patient diaries should be kept in which the type of symptoms, their duration and severity as well as adverse reactions would be recorded daily.

d. Interpretation of data. Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigations. At least one of the three studies must be in patients with chronic pulmonary disease. Approximately 20 to 30 patients will be required for the crossover study described above. Because of the marked variability in sputum production in patients with chronic respiratory disease from day to day together with the spontaneous waning of...
symptoms as part of its natural history, a much larger number of patients, possible 75 or more, must be studied for this group. The subjective indices to be evaluated can be scored for statistical analysis, with a p value of 0.05 or less (95 percent confidence level) being accepted as evidence of a drug effect when compared with placebo.

All data submitted to the Food and Drug Administration must present both favorable and adverse effects, e.g., Evaluation of safety. Tests for safety of expectorant ingredients not reviewed by this Panel should involve the usual animal studies and observations in man relevant to various organs and systems, i.e., cardiovascular, respiratory, renal, hepatic, cerebral, and hematologic. Of special note is oral as expectorant drugs may be distinct pharmacologic groups. The sympathetic amines, ephedrine and methoxymethamphetamine, are carcinogenic, effect on clotting mechanisms, thyroid function, electrolyte and acid-base balance, in addition to the general areas mentioned above.

V. BRONchodilators
A. GENERAL DISCUSSION

Bronchodilators are agents used for the symptomatic treatment of the wheezing and shortness of breath associated with chronic conditions of the nasopharynx. These drugs are also used but are much less effective in relieving the shortness of breath of chronic bronchitis and emphysema. The drugs most commonly used as bronchodilators are some sympathomimetics (sympathomimetic amines), theophylline, and the propylenes. The Panel has classified these major forms of bronchodilators, i.e., sympathomimetic amines and theophyllines, as distinct pharmacologic groups. The sympathomimetic amines and theophyllines work well when given together, but for the patient who is a rapid metabolizer of the theophylline, a fixed-dose of a theophylline and a sympathomimetic to be taken by mouth, for example, as a tablet, should be very effective and convenient. However, to obtain the most effective bronchodilation, the dose of the sympathomimetic might be individualized because of individual variation in the metabolic breakdown of theophyllines (Ref. 3).

The Panel is concerned that in a patient who is a rapid metabolizer of the theophylline, a fixed-dose of a theophylline and a sympathomimetic in an oral combination product might have reduced effectiveness because of a low theophylline dose. If the number of dosage units, e.g., combination tablets taken is increased to provide an effective theophylline dose, the dose of sympathomimetic might be excessive and cause side effects. Conversely, in a patient who is a slow metabolizer of theophylline, the standard dose of an oral combination product of theophylline and a sympathomimetic might produce theophylline toxic effects. If the number of combination tablets is decreased to avoid these side effects, then the dose of sympathomimetic might be so low as to have a low effectiveness.

Therefore, it would appear that single ingredient preparations containing either a theophylline or a sympathomimetic would be both more effective and less dangerous inasmuch as they have increased safety as compared to combination products.

Although the bronchodilators are generally safe for OTC use at recommended dosage levels, care should be taken in reducing the shortness of breath caused by bronchospasm. The Panel emphasizes that these preparations should not be used unless a diagnosis of asthma has been made by a physician and a dosage schedule of OTC medicine has been established by a physician.

Patients with asthma may also require prescription drugs which may have serious dangers and side effects and there is, then, an added need for continued medical supervision.

REFERENCES


sure in patients taking drugs containing monoamine oxidase (MAO) inhibitors.

4. Labeling. The Panel recommends the following labeling for bronchodilator active ingredient preparations. (See part V. paragraph B.1, below—Category I Labeling) In addition the Panel recommends the following specific labeling: Warnings. (i) "Cold, Flu, and Aches. Do not take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse;" (ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur." (iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland;" (iv) Drug Interaction Precaution. "Do not take this product if you are presently taking a prescription antidepressant or antihypertensive drug containing a monoamine oxidase inhibitor;" (v) "Professional labeling. The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following advice and supervision of a physician;" (vi) Professional labeling. The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following advice and supervision of a physician.

5. Dosage. Adult oral dosage is 12.5 to 25 mg not more often than every 4 hours. (See part V. dosage section discussed below."

References:


6. Epinephrine preparations (epinephrine, epinephrine bitartrate, epinephrine hydrochloride (racemic) inhaled aerosol). The Panel concludes that epinephrine is safe and effective for OTC use as a bronchodilator as specified in the dosage section discussed below.

7. Safety. Wide use of epinephrine aerosols for temporary relief of spasm that causes narrowing of air tubes has been attended by few and mild side effects. However, one early report by Benson and Ferlan (Ref. 1) raised the possibility that epinephrine aerosols caused serious harm to the lining of the air tubes, resulting in an increase in air tube secretions which in turn predisposes to infection and collapse of small areas of the lungs. However, more serious complications have not been reported. The report was retrospective and found that a greater number of deaths occurred in users of epinephrine aerosols (1.4 percent) as compared with 22 of 3,588 nonusers (1.4 percent). The possibility that the users might have had a more severe illness than nonusers was not considered and might well explain the findings.

In a study of 86 patients with various types of cardiac involvement and 16 patients with uncontrolled diabetes who inhaled aqueous epinephrine from a nebulizer (Ref. 2), no untoward effects developed following administration of many times the dose considered to be effective in asthma, nor were there significant changes in pulse rate, blood pressure, electrocardiogram, or blood sugar level. The authors conclude that the presence of diabetes is not a contraindication to the use of 1,1-epinephrine (racemic) or 1-epinephrine (levorotatory) by inhalation.

Epinephrine aerosol was used for many years before its safety was questioned. The question arose because of an increase in the number of deaths among those using a chemically related drug, isoproterenol, a prescription drug, which also caused aggravation of the airway obstruction in some patients.

The reports of an increase in deaths from isoproterenol had their origin in England (Ref. 3). A possible explanation was that the preparation used there had a concentration of isoproterenol 5 times greater than that used in Sweden, Australia, and the United States, where no such increase in deaths had been noted (Ref. 4). It was inferred that the high concentration of isoproterenol accounted for the increased death. Deaths decreased when a lower concentration of isoproterenol was used.

Aggravation of the obstructive abnormality clearly occurs in some patients with asthma following administration of isoproterenol (Ref. 5) and due to some fraction of absorbed isoproterenol being converted to a metabolite which could predispose to causing spasm of air tubes (Ref. 6).

It has been further observed (Ref. 7) that isoproterenol by inhalation, while producing bronchodilation, may simultaneously cause a small and usually clinically insignificant fall in blood oxygen level. That this has not been observed with epinephrine by inhalation may merely reflect the small amount of interest in this drug in the years since it was marketed. For most patients the necessary measurements have become readily available, but the tests have not been done. It is unlikely that these observations or toxicity, however, concerning isoproterenol are relevant in judging the safety of epinephrine by inhalation. Epinephrine stimulates both alpha and beta receptors (Ref. 8) and would be expected to have a local anesthetic effect on the blood vessels in the lungs as it does in subcutaneous tissue, an effect expected to limit systemic absorption of the administered
drug. Isoproterenol is predominantly a stimulator of beta receptors (Ref 8) and would be expected to cause vascular dilation and systemic absorption and administration. The relative therapeutic advantage or disadvantage of this difference between the two drugs is unknown and needs further study.

One additional difficulty may arise which applies to all sympathomimetic drugs self-administered by inhalation for relief of asthma. A patient with severe and worsening obstructive pulmonary disease may obtain very temporary relief and this relief may give a false sense of security. Under such circumstances the patient may postpone calling a physician and worsening obstructive pulmonary disease could not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if used.

Labeling. The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling for preparations of epinephrine used by inhalation: Warnings. (i) Do not take this product at a higher than recommended dose except under the advice and supervision of a physician. There is the possibility of abuse of this material and possible adverse effects on the heart if used.

(ii) Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.

(iv) Drug Interaction Precautions. Do not take this product if you are presently taking any other sympathomimetic or antidepressant drug containing a monoamine oxidase inhibitor.

(v) Keep this product out of reach of children.

(vi) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(vii) “Do not give this product to children under 4 years, there is no data on the use of this drug in children under 12 years are available. But there is still been limited clinical experience with this drug in children. The Panel concludes that methoxyphenamine should not be used in children under 12 years.”

(viii) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(ix) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(x) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xii) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xiii) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xiv) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xv) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xvi) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xvii) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xviii) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xix) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xx) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xxi) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xxii) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xxiii) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xxiv) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xxv) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xxvi) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xxvii) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”

(xxviii) “Do not give this product to children under 4 years except under the advice and supervision of a physician.”

(xxix) “Do not continue to take this product if you have the following symptoms: (a) frequency of complaints of side effects except under the advice and supervision of a physician.”


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"Caution: Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse.

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur."

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or urination problems due to enlargement of the prostate gland".

(iv) "Drug Interaction Precaution. Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

**References**


**d. Theophylline preparations (a-amino-phenyl theophylline, theophylline anhydrous, theophylline calcium sulfate, theophylline sodium glycinate).** The Panel concludes that the theophylline preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below when the dosage is based on the anhydrous theophylline equivalent.

1. **Safety.** The most commonly encountered adverse effects of theophylline—anorexia, nausea, and vomiting—are attributed to central nervous system effects. Whether administered orally as uncoated tablets, by injection, or rectally, gastrointestinal symptoms in adults and children are usually negligible if whole blood levels of theophylline do not exceed 8 µg/ml (equivalent to plasma levels of 15 µg/ml). The corresponding plasma level is greater because theophylline does not enter the brain (Refs. 1-7).

2. **Gastrointestinal symptoms** were associated with orally administered aminophylline (theophylline ethylenediamine) when whole blood levels of theophylline exceeded 11 µg/ml (equivalent to plasma levels of 20 µg/ml) (Ref. 1).

Aminophylline administered as an uncoated tablet or theophylline as an alcoholic elixir is quite rapidly and reproducibly absorbed within 1 hour from an empty stomach. Thus, oral absorption and tissue response to a given concentration of theophylline is dependent on the rate of renal excretion. At plasma levels of 20 µg/ml (equivalent to plasma levels of 8 to 10 µg/ml), theophylline is internally quite stable in terms of rate absorption and variability in extent of absorption (Refs. 5 and 7). However, recent studies showed that food makes little difference in the absorption of theophylline provided the tablet has a satisfactory disintegration time (Ref. 6). Studies of theophylline indicate that variations between patients in their maintenance dose requirements are attributable to remarkable differences in the rate at which theophylline is metabolized. In one study of 83 patients, oral aminophylline dosage ranged from 400 to 5,200 mg/24 hours in order to maintain therapeutic blood levels. About 10 percent of patients receiving 300 mg every 4 hours for at least 48 hours experienced loss of appetite, nausea, and vomiting. Therefore, patients should be helped to adjust their aminophylline dosage to variations in rate of theophylline metabolism between patients, each individual is internally quite stable in terms of rate of handling this drug so that it is possible to adjust to individual effective dose for continued therapy (Ref. 1).

In children, oral doses of aminophylline of 4 to 5 mg/kg every 8 hours (50 percent of aminophylline calculated as the free base) is recommended as generally devoid of undesirable side effects (Refs. 8 and 9). Severe toxicity in children may include vomiting with blood in the vomitus and dehydration, central nervous system stimulation leading to convulsions and coma, and cardiovascular collapse. The majority of literature reports of theophylline and aminophylline toxicity in children, and particularly those resulting in death, have been associated with use of aminophylline suppositories. Administered dosage of theophylline in these cases ranged from a normal dosage of 10 mg/kg/24 hours to 75 mg/kg/30 hours (Refs. 8 and 10 through 20). Analysis of the cases of toxicity with recommended dosage of suppositories and the concurrent oral or parenteral administration of a theophylline preparation. Because of the toxicity potential from overdose unless the dose is individualized to the needs of a child on a mg/kg basis, the Panel believes that such OTC products should not contain labeling with a recommended dose for children.

Aminophylline, due to its ethylenediamine content, may produce a contact-type dermatitis upon systematic administration to individuals previously sensitized to the topical application of ethylenediamine (Ref. 30).

2. **Effectiveness.** Following intravenous aminophylline in a variety of patients with narrow caliber airways caused by spasm, the dosages of theophylline were effective "trough" levels (middosing blood levels) of theophylline in the 5.5 to 11 µg/ml range. These authors recommend 200 mg aminophylline (240 mg anhydrous theophylline) every 6 hours, 4 times daily (Ref. 11). Following 120 mg doses, blood levels at best reach 4.3 µg/ml (equivalent to plasma levels of 7.6 µg/ml) (Refs. 1, 3, and 31 through 33). Since the blood level attained and maintained in a given patient is dependent on drug metabolism rates, which varies among individuals, an OTC dose recommendation of 100 to 200 mg of anhydrous theophylline equivalent should be based on patients individualize the dose for optimal response yet minimize side effects.

The Panel recommends that scored tablets in dosage units of 50 mg, 100 mg, and 200 mg be made available for OTC use. The Panel is concerned that theophylline tablets be readably absorbed when ingested. All tablets must pass a satisfactory disintegration test. The Panel recommends that each tablet formulation be tested according to the procedures described in the United States Pharmacopoeia XIX (Ref. 34). The tablets shall be considered satisfactory for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount (based on anhydrous theophylline equivalent content) and the quantity of theophylline dissolved within 30 minutes is not less than 70 percent of the labeled amount (based on anhydrous theophylline equivalent content) for any of the tablets tested. The resulting data shall be submitted to the Food and Drug Administration prior to marketing.

A double-blind controlled study in 300 asthmatic children ages 6 to 12, receiving 150 mg theophylline by mouth in plain capsules correlated with significant improvement as measured by pulmonary function tests with theophylline blood levels greater than 3.2 µg/ml (equivalent to plasma levels of 6 µg/ml) (Ref. 3).

A review of oral theophylline drugs lists the anhydrous theophylline equivalents in various proprietary preparations (Ref. 29). For purposes of standardization, the dosage recommendations of the Panel are based on anhydrous theophylline equivalent content.

3. **Dosage.** Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 120 mg every 6 hours, not to exceed 800 mg in 24 hours. Children 8 to 12 under 12 years oral dosage is identified in the labeling section discussed below under professional labeling. For children...
under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warnings. (i) "Do not exceed recommended dosage except under the advice and supervision of a physician." (ii) "Do not take this product if nausea, vomiting or restlessness occurs." (iii) "Caution: Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse". (iv) "Do not take this product if you are presently taking a drug or suppository containing any form of theophylline except under the advice of a physician.

(v) Professional labeling. The Panel recommends that scored tablets should be generally recognized as safe and effective for the treatment of asthma, but are not safe and effective for use in the treatment of asthma in children.

References
(3) Miller, J. K., "Evaluation of Serum Theophylline Levels in Subjects with Bronchial Asthma after Inhalation of Theophylline. Effect of Unpublished Data" is included in TGO Volume 402358.

Category I Labelling

The Panel recommends the following Category I labeling for bronchodilator active ingredients to be generally recognized as safe and effective or as misbranded as well as the specific labeling discussed in the individual ingredient statements.

a. Indications. (1) "For temporary relief of bronchial asthma".
(2) "For symptomatic control of bronchial asthma".
(3) "Provides temporary relief from acute symptoms of bronchial asthma".
(4) "Relaxes tense bronchial muscles to ease breathing for asthma patients".
(5) "For temporary relief of wheezing (attacks and distress) of bronchial asthma".

b. Warnings. (1) "Caution: Do not take this product unless a diagnosis of asthma has been made by a physician." (2) "For symptomatic relief of bronchial asthma".

Category II Conditions under which bronchodilator ingredients are not generally recognized as safe and effective or as misbranded:

B. Belladonna alkaloids

Pseudoephedrine preparations: Pseudoephedrine hydrochloride, Pseudoephedrine sulfate.

a. Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonium). The Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxicity. In view of the availability of other safer and effective OTC drugs for the treatment of asthma, the Panel concludes that there is no place for this preparation in the OTC treatment of asthma.

b. Safety. A mixture of stramonium and belladonna is available and is utilized by smoking the cigarettes or pipe mixture or by burning the powder, like incense, and inhaling the smoke. For oral use (cigarette, pipeful, etc.), the alkaloid content presumably absorbed systemically is about 0.125 mg (Refs. 1 and 2). However, the preparation is easily abused for its psychoactive properties, by excessive use or ingestion of dry pet- retes, liquid suspensions or capsules filled with the powder (Ref. 2). Intoxication is generally characterized by confusion, delirium, hallucinations, and various anticholinergic effects, such as difficulty in swallowing due to dry mouth, blurred vision, photophobia, difficulty in urination, and constipation. Some deaths have been reported (Ref. 2). The adverse effects of excessive use of the powder have been well described (Ref. 3). There are numerous reports of intoxication us-
ing the powder or ingesting seeds or leaves of stramonium plants (Refs. 4 through 9). Clearly, products containing belladonna alkaloids present a risk to the consumer.

(2) Effectiveness. Belladonna alkaloids may be of benefit when given in the form of cigarettes (Ref. 9), but there has been no critical assessment of effectiveness. There are no well-controlled studies or other evidence to support its effectiveness as a bronchodilator when used by inhalation in the treatment of asthma.

(3) Evaluation. The Panel concludes that the effectiveness of belladonna alkaloids by inhalation is unproven. In view of the high potential for abuse and toxicity and the availability of other safe and effective drugs, the Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma.

REFERENCES


(3) Talatiero, L., "Asthmatoid," Draft of unpublished article is included in OTC volume 404998.


b. Pseudoephedrine preparations (pseudoephedrine hydrochloride, pseudoephedrine hydrobromide). The Panel concludes that pseudoephedrine preparations are safe but not effective for OTC use as a bronchodilator.

(1) Safety. In a study of cardiovascular effects of pseudoephedrine, dose response in four subjects showed that 210 to 240 mg (3.0 to 4.0 mg/kg) were required to raise diastolic blood pressure to 90 mm Hg or above (Ref. 1). However, a serious rise in blood pressure may occur if the drug is taken concurrently with monoamine oxidase (MAO) inhibitors (Refs. 2 and 3). Skin reactions both of long and short duration may be associated with the drug but these are rare (Refs. 4 and 5). Six of 21 patients who took 60 mg orally had mild side effects of dryness, nausea, insomnia, and headache (Ref. 6).

(2) Effectiveness. In a careful double-blind study using 210 mg pseudoephedrine hydrochloride orally in nine subjects with reversible obstruction to air flow, measurements were made of vital capacity and forced expiratory volume in 1 second (FEV₁), which is a measurement related to airway obstruction, the higher the better. The study figure the better the air flow and the less the obstruction in the air tubes (Ref. 1).

High dose of pseudoephedrine increased FEV₁ to less than half that produced by an equivalent dose of ephedrine (Ref. 2). The mean percentage increased in FEV₁ was only 11 percent after pseudoephedrine and this is within the variation of the test and does not show a significant change. Ephedrine was used in the same study of 150 mg and caused a 27 percent improvement in FEV₁. In another double-blind placebo-controlled study, 100 to 200 mg of pseudoephedrine was given intravenously and was ineffective in 12 human subjects as a bronchodilator as judged by changes in forced vital capacity (FVC) and forced expired volume (FEV₁) (Ref. 7).

(3) Evaluation. Based on the two studies reviewed (Refs. 1 and 7), the Panel concludes that pseudoephedrine is ineffective for the consumer and therefore cannot be generally recognized as effective in the treatment of asthma.

REFERENCES


Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling (see part II, paragraph O above—COMMUNICATING CLAIMS NOT SUPPORTED BY SCIENTIFIC EVIDENCE). However, labeling that is descriptive of the product such as Its taste or appearance are acceptable.

The Panel concludes that the following labeling is misleading and contains unacceptable claims for preparations used for the treatment of asthma. The Panel assumes that the preparation under consideration will contain only a sympathomimetic of the bronchodilator type and/or theophylline ingredients. The Panel believes that the language expressed in the following misleading claims is excessive and results either too much or ineffective effects which do not occur. For example, most asthma preparations have no effect on hay fever, the nose, the "common cold", or on congestion. The following apply regardless of whether the preparation is given by inhalation or by mouth:

a. Unacceptable labeling because these effects do not occur on bronchodilators. (1) "Relief of hay fever."

b. Claims for any effects on nasal passages.

c. Statements related to "congestion of air tubes or lungs."

(2) "Decongests swollen membranes, acts to loosen congestion—relief of general respiratory congestion."

(3) "Relief of bronchitis or 'the common cold'".

(4) "Relief of fear, anxiety, nervous tension."

(5) "Cleans bronchial passages."

(6) "Contains anti-allergen ingredient."

(7) "Eases irritation of bronchial and nasal mucous membranes, and itchy, watery eyes."

(8) "Relief of other respiratory conditions."

(11) "Pseudophedrine preparations because the claim suggests it is particularly effective."

(12) "Nagging cough is reduced to a minimum and as a result sleep is much deeper and interrupted."

b. Unacceptable labeling because of the difficulty to substantiate and the implication that high use rate is evidence of the particular effectiveness of the ingredients. "Most prescribed or recommended by doctors in medical practice."

c. Unacceptable labeling because excessive claims are made in emotional terms.

(1) "Relieves gasping for air."

(2) "Free breathing restored."

(3) "Breathe a sigh of relief."

3. Category III conditions for which the available data are insufficient to permit final classification at this time. The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredient and conditions listed below. The Panel believes it is reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredient and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as a bronchodilator must be demonstr-
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1. Principles in the design of an experimental protocol for testing bronchodilator drugs. a. General principles. The effectiveness of a bronchodilator drug is determined by its ability to reverse the airway obstruction of patients with asthma. Although clinical improvement may be reported, it is essential to have objective measurements of pulmonary function to substantiate improvement. Tests of bronchodilator drugs should be double-blind and crossover studies. Pulmonary function tests should be performed before and after the drug or placebo is given. Objective testing should be done for a sufficient time to show the duration of action of the drug. For OTC drugs a single dose should be shown to be effective. Continuing taking of the drug over several days to show improvement is not acceptable for OTC products. The patient needs to get quick and obvious relief from a single dose. The drugs used should be tested in the same dosage as the purchasers might be expected to take, i.e., the recommended dosage on the label.

To show effectiveness it is necessary for two studies by two different investigators to show a mean difference of definite improvement in pulmonary function following single doses of the drug under test as described under Interpretation of data, below.

b. Selection of patients. Selection of patients for testing should be based on the diagnosis of asthma. There should be generalization airway obstruction whose severity varies greatly over short periods of time, and this should be demonstrated by pulmonary function tests improving significantly after the use of an accepted bronchodilator drug.

c. Methods of study. For a series of patients, the forced vital capacity, forced expiratory volume (one second), and maximal mid-expiratory flow rate are the simplest and most available tests. However, maneuver's of flow from flow-volume curves at 50 percent and 75 percent of the vital capacity, measurements of airway resistance in two specific conductance using a body plethysmograph are recommended when the complex equipment is available.

The precise number of patients to be tested cannot be stated. However, if the drug is effective, approximately 20 patients should be sufficient for satisfactory statistical analysis of data.

d. Interpretation of data. Ideally, the response should be interpreted according to the recognized variability in the laboratory in which the test is being performed. Where such variability is not precisely defined, improvement of 15 to 25 percent may be considered a slight reversibility; a change of 26 to 50 percent is moderate reversibility; and greater than 50 percent is marked reversibility. However, for the purposes of an experimental protocol, statistical analysis and significance is "skeletal."

Evidence of drug effectiveness is required from at least a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must be presented with favorable and unfavorable results.

e. Evaluation of safety. Tests of safety should involve the usual tests for toxicity to the respiratory system and be relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to maximum therapeutic effectiveness.

REFERENCES


VI. ANTICHOLINERGICS

A. GENERAL DISCUSSION

Anticholinergics are drugs used in the treatment of relief of excessive secretions of the nasal passages, commonly associated with hay fever, allergy, rhinitis and the "common cold."

The tissues responsible for these secretions, the glands of the nasal mucosa and
the lacrimal glands, are supplied by nerves known as parasympathetic or parasym pathetic nerves. These nerves release a neurohumoral substance, acetylcholine (ACh), which acts on receptors in these tissues apparently causing the excessive secretions by competing with ACh for these receptors, reduce or prevent the secretions.

There are other tissues having receptors active to ACh. The anticholinergic drugs are able to prevent the response usually caused by ACh at these sites as well. These other tissues are the sweat, salivary and bronchial glands, the muscles of facial and visual accommodation (adaptation of the eye for distinct vision at different distances), the heart, the gastrointestinal tract, and the urinary bladder. The cholinergic nerves which innervate these tissues are com- positionally known as the parasympathetic nervous system. All these tissues are not equally sensitive to the anticholinergic agents and the responses are dose-related. Small doses depress salivary bronchial and sweat secretions. Larger doses are required to inhibit visual accommodation or increase the heart rate. Still larger doses are required to inhibit the parasympathetic control of the gastrointestinal tract or the urinary bladder. The naturally occurring anticholinergic drugs, such as those from the belladonna plants, are widely distributed in nature especially among the Solanaceae. The active drugs derived from these plants are atropine (dl-hyoscyamine) and scopolamine (1-hyoscine) depending upon which plant is the source. The official preparations of belladonna act chiefly by virtue of their atropine content.

Atropine is the classical representative of this group of anticholinergic drugs. It is dl-hyoscyamine, the stereoisomers being present in equal amounts but the activity residing in the l-form. The drying effect on the respiratory tract may be useful in the symptomatic relief of excessive secretions of the nose (rhinorrhea) and eyes commonly associated with hay fever, allergy, rhinitis and the "common cold." The atropine in excessive atropine is not noticeable if there are excessive secretions. There is no evidence that the course of the illness is altered by these drugs. At higher doses, the bronchi and broncholi are normal for the respiratory airways are relaxed. This relaxation is most pronounced if the bronchi and broncholi are contracted by histamine or increased parasympathetic activity and the atropine is administered by inhalation.

These drugs reduce the volume of secretions as well as making them less fluid. The less fluid secretions are more difficult to remove from the respiratory airways and may lead to obstruction. This predisposes the patient to infection. In a person with bronchial asthma or chronic obstructive pulmonary disease, this may be extremely hazardous.

The belladonna alkaloids will have little effect on the intraocular pressure of the normal eye. However, in the glaucoma, elevation of the intraocular pressure is initially above normal, they are likely to increase the intraocular pressure and damage the eye, especially in narrow angle glaucoma.

The toxic or side effects of the anticholinergic drugs are an extension of the pharmacologic effects of the drugs. These effects are dry mouth, anhydrosis, tachycardia, palpitation, impaired vision, photophobia, restlessness, confusion and difficulty in urination. Very large doses may cause elevated body temperature and respiratory depression. Elderly men with enlargement of the prostate gland may develop urinary obstruction with less than toxic doses. There are numerous synthetic anticholinergic compounds, none of which differ significantly in pharmacologic effects or toxic effects from the naturally occurring drugs. Antispasmodic drugs are discussed in another section of this document. (See part VII. below.—Antispasmodics.) Given together with an anticholinergic in the same preparation or at the same time, an antihistamale drug will have at least an additive anticholinergic effect. With this in mind, the dose of each should be adjusted accordingly.

References


B. CATEGORIZATION OF DATA

1. CATEGORY I conditions under which anticholinergic ingredients are generally recognized as safe and effective and are not misbranded.

Category I Active Ingredients

The Panel was unable to classify a claimed anticholinergic active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for anticholinergic active ingredients to be generally recognized as safe and effective and not misbranded:

a. Indications. (1) "For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract."
(2) "Temporarily suppresses watery nasal discharge."
(3) "Temporary relief from excessive nasal secretions."
(4) "Temporary relief from running nose."
(5) "Temporarily suppresses watering of eye."

b. Warnings. (1) "Do not exceed recommended dosage except under the advice and supervision of a physician."
(2) "Do not continue to take this product if condition is not improved in 1 to 3 days.

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The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of products is unsupported by scientific data, in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until further testing is completed.

Category II Active Ingredients

The Panel has classified the following anticholinergic active ingredient as not generally recognized as safe and effective or as misbranded:

The Panel concludes that belladonna alkaloids (as contained in Atropa belladonna and Datura stramonia) when used by inhalation are not safe and effective for OTC use in asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxic-
The Panel concludes that the following claims are misleading and are unacceptable for preparations used as anticholinergics:

a. Claims not supported by scientific data. "Clears nasal passages, open airways".

b. All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies. These include claims such as "specially formulated...imparts its own selected...natural", "extra strength", "teamd components", "superior to ordinary", also claims implying a physiological effect which either has no foundation or meaning or will be meaningless or misleading to the public such as "anti-allergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", and "travels through the blood stream".

c. Claims for relief where time is indeterminate, and not supported by scientific data. These include claims such as "all day", "all night", "for hours", "fast", and "prompt relief".

3. Category III conditions for which the available data are insufficient to permit final classification at this time. The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to permit these ingredients and conditions listed below. The Panel believes it reasonable to permit these ingredients and conditions to be investigated in order to determine the safety and effectiveness of atropine sulfate as an anticholinergic. In the treatment of excessive secretions of the nose associated with the "common cold," atropine appears to be ineffective, but only one study is available (Ref. 6). The study indicated that 0.6 mg of atropine given every 6 hours may transiently reduce the nasal secretions associated with the "common cold" giving some temporary comfort. However, there is no evidence that the very small dose of belladonna alkaloids per dosage unit in currently marketed OTC preparations, i.e., 0.03 to 0.2 mg total belladonna alkaloids, are effective.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of atropine sulfate as an anticholinergic. The Panel concludes that adequate and reliable data are not obtained at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to permit these ingredients and conditions to be investigated in order to determine the safety and effectiveness of atropine sulfate as an anticholinergic. In the treatment of excessive secretions of the nose associated with the "common cold," atropine appears to be ineffective, but only one study is available (Ref. 6). The study indicated that 0.6 mg of atropine given every 6 hours may transiently reduce the nasal secretions associated with the "common cold" giving some temporary comfort. However, there is no evidence that the very small dose of belladonna alkaloids per dosage unit in currently marketed OTC preparations, i.e., 0.03 to 0.2 mg total belladonna alkaloids, are effective.

(3) Proposed dosage. The Panel is unable to determine a proposed dosage. Although 0.6 mg atropine sulfate may be effective, the Panel concludes that such a dosage should not be available for OTC use until studies demonstrate safety. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to the suitable proposed dosage. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product. In such a case, the Panel concludes that for children under 12 years, there be no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part IV, paragraph B.1. above—Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing anticholinergic drugs. (See part VI, paragraph C. below—Data Required for Evaluation.)

REFERENCES


PROPOSED RULES


(6) Personnel of the U.S. Naval Medical Research Unit No. 4, "The Prophylaxis and Treatment of Acute Respiratory Diseases with Antihistaminic Drugs," Journal of Laboratory and Clinical Medicine, 30:605-609, 1951.

b. Belladonna alkaloids. The Panel concludes that the belladonna alkaloids are probably safe in the dosage range used as anticholinergics but there are insufficient data to permit final classification of their effectiveness for OTC use as anticholinergics.

(1) Safety. Clinical experience has confirmed that belladonna alkaloids are safe in the dosage ranges used as anticholinergics. The belladonna alkaloids contain atropine (dl-hyoscyamine) and scopolamine (1-hyoscine) and are present in the official preparations e.g., belladonna tincture United States Pharmacopeia (USP) and belladonna extract National Formulary (NF). These preparations act by virtue of their atropine content, which is in the range of 10 percent of the total alkaloid content and has the same pharmacological effects and toxicity as atropine, but is slightly more potent. The Panel believes it possible to determine the safety of atropine elsewhere in this document. (See part VI, paragraph B.3.a. above—Atropine sulfate.)

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of belladonna alkaloids as anticholinergics. Atropine and other belladonna alkaloids and substitutes reduce secretion in both the upper and the lower respiratory tract, and they are common constituents of proprietary "cold" tablets (Ref. 1). This effect in the nasopharynx may provide some symptomatic relief of acute rhinitis associated with conditions such as coryza or hay fever. However, there are no controlled studies to support this hypothesis.

The belladonna alkaloids can induce bradycardia and dilatation. This effect is usually not marked when they are administered by inhalation, but it is still less than can be achieved by other types of medication.

All antimuscarinic agents reduce the volume of bronchial secretion which results in decreased fluid and implosion of the residual secretion. This viscid material is difficult to remove from the respiratory tree, and its presence can dangerously obstruct airflow and predispose to infection. Because of the effect on bronchial secretion, repeated administration of any antimuscarinic to a patient with chronic bronchitis should not be considered as potentially hazardous.

(3) Proposed dosage. Adult oral dosage is 0.2 mg 2 times daily. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part VI, paragraph B.1. above—Category I Labeling.)
(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for anticholinergic drugs. (See part VI, paragraph C, below—Data Required for Evaluation.)

REFERENCE


Category III Labelling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for anticholinergic drugs. Additional data are required to support the following anticholinergic claim: a. Prophylactic relief by helping to prevent further swelling and irritation.

b. The Panel concludes that claims relating to claims of action, e.g., "all day," "all night," "for hours," will require documentation.

c. Claims that sleep will be facilitated. These include claims such as "helps you fall asleep" and "for restful sleep."

d. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. Principles in the design of an experimental protocol for testing anticholinergic drugs. a. General principles. The effectiveness of an anticholinergic drug should be determined by the ability to reduce rhinorrhea (excessive watery nasal secretions) in patients with acute or chronic rhinitis. Tests should involve double-blind placebo controlled assessment of the ability of the drug to decrease watery nasal secretions and/or tearing when administered orally and increase the time between applications when topical applications are used. Each trial must be a subjective one since there is no technique for objective measurements. The dosage, intervals of administration and conditions for the trials should be identical to the labeled recommendations.

b. Selection of patients. Selection of patients for treatment should be based on the diagnosis of rhinitis with rhinorrhea. Patients with chronic allergic or vasomotor rhinitis may present more stable symptoms but in patients with most patients rhinorrhea is a variable and inconsistent symptom. In addition, a large number of suitable patients, e.g., approximately 50 subjects depending upon the protocol, must be used and assigned in a random fashion to placebo or drug groups. Further, the groups should be matched by age and sex, and if possible, by severity of symptom. It is also highly desirable to control conditions of temperature and humidity.

c. Methods of study. There is nothing in the literature concerning techniques for testing rhinorrhea and it is possible that a subjective method could be developed. It might be possible to semi-quantitatively assess the degree of rhinorrhea by weighing tissues or handkerchiefs; the weight increase divided by the square root of the amount of secretion per unit of time. The subjects should be evaluated on the basis of the severity of the rhinorrhea and the subjective appraisal of the patient's comfort. Numerical values should be assigned indicating increasing severity. A double-blind technique is used for patients with acute rhinitis and for chronic rhinitis with rhinorrhea. A double-blind crossover design is required. Observation should be carried out for 3 to 5 days to determine the extent of possible side effects.

2. Interpretation of data. The data should be subjected to statistical analysis with a value of 0.05 or less would be acceptable as evidence of drug action. Evidence of drug effectiveness is required by pyrilamine maleate. The positive studies based on the results of three different investigators or laboratories. All data submitted to the Food and Drug Administration in pollens in the environment both favorable and any unfavorable results.

e. Evaluation of safety. Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse reactions. These tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

VII. ANTHISTAMINES

1. GENERAL DISCUSSION

Development. The antihistamines were developed in France from a series of compounds with pronounced antihistaminic activity in the laboratory but which were too toxic for clinical use. One of these antihistaminic drugs, Antergan, was used for the first time clinically in 1942 in France. This was promptly followed by many other compounds. Antergan then followed in 1946 the appearance in the United States of diphenhydramine and tripelennamine (Ref. 1). Many active antihistamine drugs appeared soon after this time. The total number currently marketed is probably now close to fifty.

REFERENCE


2. Mechanism of action. The antihistamines are useful primarily for the symptomatic relief of certain allergic disorders (Refs. 2 through 8). They suppress the symptoms presumably by the release of histamine and possibly other chemical mediators from mast cells in mucous membranes (Refs. 1, 2, 5, and 6). Histamine attaches to specific receptor sites at the surface of cells in the nose, eyes, lungs, and skin and causes characteristic "allergic" symptoms. The antihistamines appear to act by competing with histamine for the receptor sites. If the antihistamine reaches the receptor site first, histamine is blocked from initiating a response. In this manner, antihistamines effectively block most smooth muscle responses to histamine.

The antihistamines are well tolerated by laboratory animals and produce recognizable effects on blood pressure, heart rate or respiration when given in large oral doses. These effects are more pronounced if the drugs are given intravenously (Refs. 2 and 5).

In man, the involvement of renal (kidney), respiratory, and cardiac systems is most pronounced and of particular importance is the cardiac response. The postganglionic sympathetic (blood) or other major body systems in adverse reactions appears to be remarkably uncommon (Refs. 5 and 7).

In the skin of man, antihistamines influence blood flow, such that a reaction which occurs within a few minutes after the injection of histamine intracutaneously (into the skin). The antihistamine drugs also inhibit similar reactions mediated by the other plasma class of immunoglobulins (antibodies), but to a somewhat lesser degree. The Panel has previously discussed the roles of antibodies in allergism in this document. (See part II, paragraph B.1 above—Allergy.) Examples of reactions mediated by antibodies of the IgE class are those produced by skin testing with allergens. The increase in the release is involved. In addition to histamine, there are other chemical mediators released in IgE mediated reactions, and the antihistamine drugs antagonize these much less effectively if at all. It is probably for this reason that these drugs are more active in protecting against the effects of injected histamine than in protecting against anaphylaxis in animals or allergic symptoms in man.

REFERENCES


3. Preclinical studies. As a group the antihistamines have the capacity to decrease or suppress effects produced by histamine in animals (Refs. 1 through 6). Animal "models" are those used in determining drugs which will have antihistaminic activity. An animal commonly used is the guinea pig. Guinea pigs can be protected by an antihistaminic drug from the narrowing of the air passages in the lung (bronchoconstriction) produced by histamine which causes death by asphyxia. Likewise, contraction of isolated tissues

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of the guinea pig intestine (ileum) and of the airways of the trachea and bronchiocles produced by histamine is prevented by antihistamines in vitro studies. These effects are most easily demonstrated in the guinea pig because of the animal’s intense sensitivity to histamine but the antihistaminic drugs also act in a similar manner in some other laboratory animals and in man (Refs. 1 through 3).

The antihistaminic drugs are somewhat proteiform. In experimental allergic reactions (anaphylaxis) but their action here is not so intense as their action against histamine. Apparently in man, some allergic reactions (hay fever and hives) are caused by histamine in large part by histamine release whereas other reactions, for example asthma, are not. The capacity to block the symptom-producing effects of histamine, antihistamine drugs can protect against the spasmogenic activity of histamines; 5-Hydroxytryptamine and Antagonists," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 652-664, 1970.


4. Common side effects. Among the antihistamines, there are minor differences in the nature and frequency of side effects and toxicity which are related to the chemical heterogeneity of the compounds (Refs. 1 through 3). With the exception of phenindamine, all the antihistamines considered by the Panel cause central nervous system depression, often recognized as drowsiness (sedation). Drowsiness is most marked among the antihistamines from the chemical class known as the ethanamines, e.g., diphenhydramine, doxylamine and "Phenindamine Tartrate.")

(d) Phenindamine tartrate.

The capability to cause central nervous system depression, often recognized as drowsiness (sedation) and dizziness is most marked among the antihistamines from the chemical class known as the ethanamines, e.g., diphenhydramine, doxylamine and "Phenindamine Tartrate." 5-Hydroxytryptamine and Antagonists," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 652-664, 1970.


5. Reduction of nasal secretions. A common but variable action of the antihistaminic drugs is their anticholinergic effect of reducing nasal secretions. Some patients describe this as a disagreeable drying effect. In the opinion of the Panel, the drying effect of most antihistamines is less intense than that of atropine. This action appears to be entirely palliative and does not alter or shorten the course of the illness. The Panel is aware that a controversy exists concerning the use of antihistamines in patients with bronchial asthma where a "drying action" is undesirable. Many physicians consider this effect to be disadvantageous in patients with bronchial asthma and some maintain that the antihistaminic drugs are contraindicated in patients with this disease.

It is the view of the Panel that in the presence of allergic rhinitis and in the "common cold," secretions are often excessive and a "drying" agent may then be appropriate. However, as do other investigators, that effectiveness of antihistamines widely used in the "common cold" has not been demonstrated in controlled studies (Ref. 1).
addition, the Panel concludes that there is no evidence that there is a role of histamine is either the cause of symptoms in the "common cold" nor is histamine release a significant factor in the "common cold." This will be discussed more fully below. (See paragraph C. below—Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold.")

Reference


6. Human toxicity. Unlike other classes of drugs, the extensive clinical experience with antihistamines has fairly well identified virtually all of the central nervous system manifestations of toxicity. The Panel has extensively reviewed these known toxic symptoms. While many of the more severe symptoms of antihistamines are relatively rare or are due to large doses or accidental overdose, the Panel has included them in the interest of completeness of this review.

Although rare, the data on fatal doses cause fixed, dilated pupils; muscular twitching followed by convulsions, sometimes with opisthotonos; coma; circulatory collapse; and respiratory failure. Convulsions may occur for 24 hours, coma for several days. Death rarely occurs later than 24 hours after ingestion unless due to infection associated with anagranulocytosis (Ref. 1). Because of the unique nature and wide use of antihistamine drugs and because of the lack of extensive well-controlled clinical studies, the Panel has reviewed adverse reaction reporting systems to obtain a better understanding of the safety of antihistamines. Two major sources of data are the adverse reaction files of the Food and Drug Administration and the latest Poison Control Studies of the National Clearinghouse for Poison Control Centers. Since antihistamines have been extensively marketed for nearly 30 years, the Panel believes that a review of adverse reaction reports will serve as an indication of their safety.

It should be emphasized that these information sources are not entirely accurate nor do they necessarily give a valid picture of the incidence or prevalence of particular side effects. However, these reporting mechanisms do highlight the types of adverse reactions that can be expected. Where massive overdoses are ingested, such as in suicide attempts, these reports give a clearer picture of an ingredient's toxicological profile, significant elements include a validity level, toxicity reactions which occur at varying dosage levels as well as dosage levels at which reversibility of an ingredient's toxic effects may occur.

The latest "Control Statistics," published by the National Clearinghouse for Poison Control Centers provides the latest published data now available and covers the period from January to December, 1973. This publication presents collective toxicity data on household products and medicines from the Nation's 560 Poison Control Centers. This information reflects the treatment or response to each telephone inquiry to the Poison Control Centers concerning a poisoning or accidental ingestion and is not a record of drug misuse or abuse except for the more obvious incoherencies. Although only 1973 statistics were reviewed in detail by the Panel, that particular year is considered representative of all the years for which this type data was compiled.

Unlike the Poison Control Center data the adverse reaction data compiled by the Food and Drug Administration are cumulative and represent the total number of reported cases since the reporting system was implemented in 1968. Adverse reactions are reported to the agency in a variety of ways and at various levels of sophistication. These sources include hospitals, physicians, pharmaceutical manufacturers, consumers, or Food and Drug Administration personnel who often obtain these reports from consumers and physicians. While some of the data are verified for accuracy, they are often incomplete. Data are reported having one of three relationships: directly related, probably related, possibly related and unrelated. For the Panel's purposes, only the adverse reactions which are directly or probably related to drug ingestion are discussed. The Panel recognizes that the statistics generated by the Poison Control Center and the Food and Drug Administration can be used to identify and must be carefully used in determining the potential health threat of ingredients to consumers because the extenuating circumstances of each individual case are not represented.

A review of these two sources reveals several variables in the collection and comprehensiveness of the data which must be taken into consideration for a realistic view of the statistics compiled. For example, in the Poison Control Center data, few of the ingestions were of a single chemical entity. Most ingestions were of multi-ingredient products identified as being fed to drug ingestion as a Category I determination. The Panel has discussed adequate design for clinical testing later in this document. (See part VII, paragraph C. below—Data Required for Evaluation.)

d. Clinical experience. If an ingredient has been subjected to uncontrolled clinical trials and has been shown to have sufficiently broad acceptable clinical use, i.e., general use and recognition by the medical community and effectiveness for the treatment of allergic rhinitis, the findings were used to support a Category I determination. The Panel has determined that some clinical use may have been acquired while the ingredient was marketed and available only by prescription but only when used for the treatment of allergic rhinitis similar to that to be encountered with OTC use.

e. Acceptable side effects. If an ingredient is shown to have side effects in man for which appropriate labeling can be established, e.g., use and warnings against unsafe use such as "May cause drowsiness," the findings were used to support a Category I determination. In considering the acceptability of these side effects, the Panel questioned whether warnings were sufficient or whether the degree of side effects, and possibility of abuse or misuse pose a problem. It also should be compensated for with adequate labeling. The Panel finds that this is an

References


7. Criteria for classification of antihistamines as Category I. In evaluating the antihistamines submitted for review, the Panel established the following criteria for classification of an ingredient as safe and effective and not misbranded for use as an antihistamine:

a. Antihistamine activity. If an ingredient has been tested in animal models and demonstrated to have antihistamine activity, i.e., in vitro test and in vivo tests (animal challenge with histamine and animal anaphylaxis protection), the findings were used to support a Category I determination.

b. Animal toxicity. If an ingredient has been tested in animals and found to have a low degree of toxicity, the findings were used to support a Category I determination.

c. Clinical studies. If an ingredient has been tested clinically and the studies have determined that adverse reactions which are directly or probably related to drug ingestion are

d. Clinical experience. If an ingredient has been subjected to uncontrolled clinical trials and has been shown to have sufficiently broad acceptable clinical use, i.e., general use and recognition by the medical community and effectiveness for the treatment of allergic rhinitis, the findings were used to support a Category I determination. The Panel has determined that some clinical use may have been acquired while the ingredient was marketed and available only by prescription but only when used for the treatment of allergic rhinitis similar to that to be encountered with OTC use.

e. Acceptable side effects. If an ingredient is shown to have side effects in man for which appropriate labeling can be established, e.g., use and warnings against unsafe use such as "May cause drowsiness," the findings were used to support a Category I determination. In considering the acceptability of these side effects, the Panel questioned whether warnings were sufficient or whether the degree of side effects, and possibility of abuse or misuse pose a problem. It also should be compensated for with adequate labeling. The Panel finds that this is an
especially important consideration for recommended dosages of ingredients higher than those currently available for OTC use, e.g., chlorpheniramine 4 mg or for ingredients previously not available for OTC use, e.g., diphenhydramine.

The Panel has summarized the findings in the following table:

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>Antihistaminic activity</th>
<th>Animal toxicity</th>
<th>Clinical studies</th>
<th>Clinical experience</th>
<th>Acceptable side effects</th>
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<tr>
<td>Brompheniramine maleate</td>
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<tr>
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<td>Dihydropyrine fumarate</td>
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<tr>
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<tr>
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<tr>
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</tbody>
</table>

d. Brompheniramine maleate. The Panel concludes that brompheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 600 million dosage units of brompheniramine maleate were sold. (See part VII, paragraph A.B. above—Human toxicity.) Of the 568 reported cases of suspected poisonings for brompheniramine maleate, 17.1 percent exhibited some symptoms serious enough to require hospitalization. The author reporting the case noted that previous investigations had reported three cases of agranulocytosis associated with thalidamine tartrate therapy (Ref. 8). The Panel concludes that the data do not substantiate that brompheniramine maleate was the causative factor in producing the blood dyscrasias. The drug has been extensively marketed and available by prescription for over 15 years without documented cases of agranulocytosis occurring.

The Panel is aware of a reported case of agranulocytosis following therapy with two antihistaminic drugs, thalidamine tartrate and parabromdylamine maleate (Ref. 7). The incident occurred in 1958 in which a 64-year-old female had taken both drugs. The drug manufacturer of thalidamine tartrate discontinued marketing the drug but within months of its reported association in the medical literature with agranulocytosis. The other drug, parabromdylamine maleate, is also known as brom- pheniramine maleate. The patient had taken 4 mg brompheniramine maleate orally 4 times daily concurrently with an antibiotic ointment for the treatment of a pruritic rash. The patient received a total dose of 568 mg brompheniramine maleate over a period of approximately 60 days. The symptoms persisted and the drug was discontinued at which time 25 mg thalidamine tartrate was given orally 4 times daily for an additional period of approximately 60 days for a total dose of 1,880 mg thalidamine maleate prior to hospitalization. The author reported the case noted that previous investigations had reported three cases of agranulocytosis associated with thalidamine tartrate therapy (Ref. 8). The Panel concludes that the data do not substantiate that brompheniramine maleate was the causative factor in producing the blood dyscrasias. The drug has been extensively marketed and available by prescription for over 15 years without documented cases of agranulocytosis occurring.
It should be noted that while brompheniramine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations for these levels in OTC use and for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that brompheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) Effectiveness. Studies in animals have shown brompheniramine to have intense antihistaminic activity and to protect against anaphylaxis (Refs. 1 and 6). In addition to its demonstrated effectiveness as an antihistamine and protection against anaphylaxis in animals, brompheniramine has been shown in double-blind studies in humans to be effective in suppressing the symptoms of allergic rhinitis in doses of 4 mg or more given at 4 to 6 hour intervals (Refs. 10 through 12).

Available evidence indicates that brompheniramine has about the same effectiveness for children as for adults (Ref. 1). In studies of the treatment of perennial rhinitis, efficacy was reported in 23 children ages 2 months to 3 years at a dosage of 1 mg orally in 24 hours divided into 3 doses (Ref. 2). Likewise, 0.2 mg/lb in 24 hours was reported as effective in 23 children ages 2 to 6 years and 0.15 mg/lb in 24 hours in 16 children ages 4 to 14 years who had received other antihistamines without benefit. In addition to treatment with brompheniramine, all had been instructed in environmental control measures and many were receiving injections of allergenic extracts. The contribution made by these measures to the reported benefit cannot be assessed. There were no controlled groups although the statement is made that the patients were selected by “alternate allocation,” the meaning of which is unclear. The statement that over three-fourths of the patients had benefited from these measures and “various other antihistaminic agents” is surprising in the light of what is known today about the efficacy of the antihistaminic drugs in rhinitis. Therefore, the Panel concludes that evidence of effectiveness for children is insufficient.

The Panel concludes that brompheniramine maleate 4 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) Dosage. Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years, oral dosage 4 to 6 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII paragraphs B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: Professional labeling. The Panel recommends that labeling provided to health professionals (to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

REFERENCES
(1) OTC Volume 040195.
(6) OTC Volume 040196.
(9) OTC Volume 040296.

b. Chlorpheniramine maleate. The Panel concludes that chlorpheniramine maleate is safe and effective for OTC use as an antihistaminic in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) Safety. The chief side effect of chlorpheniramine is sedation which occurs in 5-10% of persons taking clinically effective doses. The drug also has a mild atropine-like effect (anti-cholinergic action) in some patients. This effect might be more of a disadvantage in patients with narrow angle glaucoma. Likewise, a drying effect has been considered to be a disadvantage in patients with asthma because drying of secretions in the nasal passages may influence airflow to the airways. Data supporting these potentially adverse effects in glaucoma and asthma are not available. Overdosage with chlorpheniramine has been relatively well tolerated. Adults receiving 1.5 gm orally in 69 hours and 209 mg in a single intramuscular dose recovered from the induced side effects without incident (Ref. 1) as did a 4-year-old boy who received 175 mg orally in 3½ hours (Ref. 2).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a total of 2 billion dosage units of chlorpheniramine maleate were sold. (See part VII paragraph A.6. above—Human toxicity.) Of the 1,509 reported suspected poisonings for chlorpheniramine maleate 15.8 percent exhibited some symptoms and 5.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 14 adverse reaction reports on chlorpheniramine since 1968 (Ref. 3). Of the 14 reports, no adverse reactions were listed as being definitely related to ingestion of chlorpheniramine. Of the three listed as possibly caused by the drug’s ingestion, five were listed as possibly related to its ingestion and six were listed as remotely related to ingestion of this drug. It should be noted that chlorpheniramine is available by prescription at the 4 mg dosage level and OTC at the 2 mg dosage level. However, the safety picture presented by the prescription dosage level has given the Panel a reasonably accurate idea of what to expect from OTC marketing of the 4 mg dosage level.

The Panel concludes that chlorpheniramine maleate is safe for OTC use as an antihistaminic in the dosage range described below.

(2) Effectiveness. Chlorpheniramine has been demonstrated to be effective in animal challenge tests with histamine in anaphylaxis protection (Ref. 4). In addition, its effectiveness in doses of 4 to 8 mg 4 times daily in the treatment of perennial rhinitis is described in a number of articles and uncontrolled studies and is supported by controlled studies (Refs. 5 through 8).

In a double-blind controlled study of the effectiveness of doxylamine succinate, chlorpheniramine was included as a standard of effectiveness. In this study 7.5 mg and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 50 patients and the study extended for 1/2 days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from 7.5 or 12.5 mg doxylamine. In this study measurements of resistance to nasal air flow were made and failed to show any effect of the antihistaminic on air flow compared with the placebo (Ref. 9). Other studies corroborate this finding. Using measurements of resistance to air flow in the nose, a well-controlled study...
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to determine the effect of chlorpheniramine given in an oral dose of 4 mg on relief of nasal obstruction gave no objective evidence of any effect over a period of 4 hours (Ref. 10). There was a significant decrease in resistance to flow when pseudoephedrine was given in a dose of 30 mg, indicating that the method is capable of revealing therapeutic effect. Likewise, a study submitted in an OTC Volume showed increased nasal obstruction in patients with nonallergic acute rhinitis after 8 mg chlorpheniramine in a sustained action form (Ref. 11). Both of these studies were done in patients without evidence of allergy. These studies indicate that chlorpheniramine does not relieve and indeed, may aggravate nasal obstruction.

Only one study (Ref. 5) appears to have been done using a 2 mg dose, which is commonly used in OTC preparations, demonstrating effectiveness. The Panel concludes that chlorpheniramine maleate has not been shown to be effective for adults at 4 mg.

The Panel concludes that chlorpheniramine maleate 4 mg is the minimum effective OTC dosage for adults for the relief of the symptoms of allergic rhinitis.

Dosage. The Panel concludes that chlorpheniramine maleate 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

Labeling. The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII, paragraph B.I. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: Professional labeling. The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

REFERENCES

(1) OTC Volume 040102.
(2) OTC Volume 040118.
(3) OTC Volume 040535.
(4) OTC Volume 04062.
(9) OTC Volume 040114.
(10) OTC Volume 040123.

C. Diphenhydramine hydrochloride. The Panel concludes that diphenhydramine hydrochloride is safe and effective in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) Data on diphenhydramine has a low order of toxicity in laboratory animals (Ref. 1). Its first clinical use was in 1946.

(2) In a double-blind study in 20 males (Ref. 2) there was no evidence of interference with tests for memory, rotary pursuit, or reaction time at a dose of 12.5 mg or 25 mg, indicating that diphenhydramine may be recommended for adults on the treatment of allergic rhinitis. Clinical experience indicates that about 50 percent of persons have dryness as a side effect when 50 mg is given (Refs. 3 and 4). In some individuals, this occurs to a degree which probably impair competence in driving a car or operating machinery. An atropinoid-like effect is also frequently described by patients as a driving sensation of the mouth and nose.

Many toxicologic studies have been carried out on diphenhydramine hydrochloride. Unpublished animal studies performed with mice demonstrated the L.D.₅₀ to be 145 mg/kg and 263.0 mg/kg (Refs. 5 through 7). In rats, the L.D.₅₀ was found to be 250 mg/kg and 494.5 mg/kg. The results of these studies are very similar when different animal strains, times when the studies were run, and variations inherent under different laboratory conditions are considered (Ref. 5). Diphenhydramine hydrochloride was demonstrated to have low toxicity in all three studies. Based upon these studies the usual adult human oral dosage level of 50 mg or 0.7 mg/kg/3 to 4 times daily is ½₉₅₀ of the oral L.D.₅₀ of diphenhydramine hydrochloride in mice (the L.D.₅₀ is equivalent to at least 200 times the therapeutic dose in man) and ½₉₀ with the L.D.₅₀ in rats (the L.D.₅₀ is equivalent to at least 700 times the therapeutic dose in man) (Ref. 5).

In chronic toxicity studies dogs were given diphenhydramine hydrochloride at dosage levels of 10, 25, 40 and 60 mg/kg/day for periods up to 6 months. There were no gross microscopic pathologic changes attributed to diphenhydramine hydrochloride (Ref. 5).

Toxic psychoses from overdoses of diphenhydramine have occurred. A case of schizophrenic-like behavior was described by Nigro (Ref. 8). Possibly the earliest suicide that was reported by Dorgedore (Ref. 9).

Other Panelists also found that very high doses of diphenhydramine in infants may cause excitement and convulsions. They reviewed three cases of children under 3 years of age (3½, 1½ and 1½ years old) who took 850 mg, 800 mg and 150 to 250 mg of diphenhydramine respectively with all doses reuting in convulsions (Ref. 10). In another case, a 3-month-old baby swallowed 9 capsules (450 mg) of diphenhydramine, after which a state of excitation was observed. Phenobarbital was prescribed, and the next day, the baby was normal (Ref. 10).

They also reviewed a group of adults ranging from 18 to 72 years, who sustained fatal convulsions, excitation, toxic psychoses, coma, petit mal, or somnolence (Ref. 10).

One case involved a 73-year-old asthmatic man, weighing 145 pounds who ingested 2,800 mg (60 capsules) of diphenhydramine hydrochloride, and was comatose and in deep sleep. Approximately 16 hours later, he awoke, feeling well. He had received no medication for this symptomatology. In other cases dealing with adult fatalities, Wyngaarden and Seevers found that the ability to withstand large overdoses appears to increase with age, and the older the patient, the less the toxic manifestation shifts from the central nervous system stimulation to that of depression. But it was also seen that a 47-year-old severely asthmatic woman died in depression after ingesting only 200 mg of diphenhydramine hydrochloride. However, the death cannot be unequivocally attributed to diphenhydramine since the shock-like state observed could well have been a complication of the disease itself and could easily have been influenced by other depressant medications that were given (Ref. 9).

The Panel considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 187.4 million dosage units of diphenhydramine hydrochloride were sold. (See part VII, paragraph A.6, above—Human toxicity.) Of the 334 reported suspected poisonings for diphenhydramine hydrochloride, 37.4 percent exhibited some symptoms and 16.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were two fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 178 adverse reaction reports on diphenhydramine since 1965 (Ref. 11). Of these reports, nine were listed as definitely related to diphenhydramine ingestion, 95 were listed as probably caused by the drug's ingestion, 58 were listed as possibly related to the drug's ingestion and 16 were listed as remotely related to diphenhydramine ingestion.

A 69-year-old female who had a history of serious medical problems and...
drug ingestion was diagnosed to have agranulocytosis. Three days after termination of diphenhydramine therapy, her white blood cell count progressively climbed to normal values (Ref. 11).

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in a statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep Aid Drug Products and published in the Federal Register on December 6, 1975 (40 FR 57282). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abuse experts. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industrialized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel notes that the dosage levels of diphenhydramine currently available by prescription are comparable to those that would be available for OTC use. Therefore, no safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(3) Safety. In animal tests, diphenhydramine has an intense antihistamine action both in vitro (Refs. 1 and 12) and in vivo (Refs. 1 and 13). The drug gives protection to guinea pigs against anaphylactic shock (Ref. 12). Diphenhydramine is also effective for the symptomatic treatment of allergic rhinitis. Although no studies with a double-blind control were found, the Panel's opinion concerning effectiveness in the treatment of allergic rhinitis rests on widespread usage over a period of 30 years. A number of uncontrolled clinical studies indicate that the drug is effective in relieving the symptoms of allergic rhinitis (Refs. 14 through 16) and one study also describes reduction of whealing in the skin induced by intracutaneous injection of both histamine and allergic extracts in patients with hay fever (Ref. 17). The Panel has also found the drug to be effective for use as an antitussive, which is discussed elsewhere in this document. (See part III, paragraph B.1.c., above—Diphenhydramine hydrochloride.)

The Panel concludes that diphenhydramine hydrochloride 25 to 50 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) Dosage. Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling.

(6) Professional labeling. The Panel recommends that labeling provided to health professionals (not to the general public) may contain the following additional dosage information: Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII of the regulation governing this section—'Category I Labeling.') In addition, the Panel recommends the following specific labeling: (1) Warning. 'May cause marked drowsiness'.

(3) Professional labeling. The Panel recommends that labeling provided to health professionals (not to the general public) may contain the following additional dosage information: Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

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2. OTC Volume 04024.
11. OTC Volume 04028.

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
12.5 to 60 mg of doxylamine succinate, side effects were observed in 39 (Ref. 9). Sedation or sleepiness was noted in four patients, and vertigo in four others. No serious toxic effects were noted after use of the drug for 6 months. Sheldon et al. (Ref. 10) gave allergic patients 12.5 to 50 mg of doxylamine succinate and found that 57 percent complained of drowsiness. However, there was some tolerance, and five were list as remotely related to ingestion of doxylamine succinate.

The Panel concludes that doxylamine succinate is safe for OTC use as an antihistaminic in the dosage ranges discussed below.

(3) Efficacy. Doxylamine is highly active in the protection of guinea pigs against intraperitoneal injection of histamine (Ref. 1). Using ileum strips in vitro, marked antihistaminic action was also demonstrated. The drug was also effective in protecting guinea pigs against anaphylactic shock (Ref. 15). Clinical experience and standard scientific textbooks indicate that doxylamine is an effective antihistaminic in dosages of 12.5 to 25 mg up to 4 times daily (Refs. 3, 7, and 15).

Two double-blind clinical trials have demonstrated the effectiveness of doxylamine in a dosage of 12.5 and 25 mg up to 4 times daily in the treatment of hay fever (Refs. 16 and 18). In these studies, subjective evaluations by patients and physicians were logged and analyzed. In a third well-designed study, doxylamine was given in a dose of 7.5 mg to one group and in a dose of 12.5 mg to a second group and a placebo to a third group, all with allergic rhinitis caused by pollen. The preparations were administered 4 times a day as required for 6 days with double-blind control. There were 40 to 45 patients in each group. Both the 7.5 mg and 12.5 mg dosages gave significant relief of symptoms as compared with the placebo, with the effectiveness of 12.5 mg exceeding that of 7.5 mg (Ref. 17). The incidence of drowsiness in both the 7.5 mg and 12.5 mg groups was not different from placebo.

In a fourth well-designed study with double-blind control, 7.5 and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 6 days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of doxylamine was not significantly different from either 7.5 or 12.5 mg doxylamine. In this study, measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 17). One study ranked doxylamine 8th in a series of 13 antihistaminic drugs in human activity in man (histamine wheal test) (Ref. 18). Doxylamine has also been described as being slightly "less potent" than promethazine but having a longer duration of action (Ref. 9). An effective dosage for children 6 to 12 years of age is 6.25 mg 2 to 4 times daily (Ref. 2) or 2 mg/kg/24 hours of 60 mg/m²/24 hours divided in 4 doses.

The Panel concludes that doxylamine succinate 7.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(4) Dosage. Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 50 mg daily. Children under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years dental dosage is identified in the labeling discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(6) Professional labeling. The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years dosage is 1.5 mg to 2.5 mg (Ref. 19) not to exceed 18.75 mg in 24 hours.

REFERENCES


e. Methapyrilene preparations (methapyrillene fumarate, methapyrilene hydrochloride). The Panel concludes that methapyrilene and methapyrilene hydrochloride are safe and effective for OTC use as antihistamines in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) Safety. In animal studies, methapyrilene appears to have a low order of toxicity in laboratory animals as compared with other common antihistamines (Refs. 1 and 2). From the results of human studies, methapyrilene appears to be safe at the recommended dosage (Ref. 3). Specifically, in the Friedlander and Friedlander (Ref. 4) study, 177 patients, one or more side effects, usually mild in nature, were encountered in approximately 25 percent of the patients receiving methapyrilene hydrochloride. These occurred most often when doses of 100 mg were administered but usually abated after the initial treatment and seldom affected the continued use of the drug. In most cases, a reduction in dosage to 50 mg obviated the side effects without modifying the effectiveness. Drowsiness, the most common side effect, occurred in 12 percent. Vertigo, headache, nausea and vomiting, diarrhea, and excessive dryness of mouth were next in order of frequency. No serious toxic effect was observed in any patients in this group receiving a daily dose of 200 to 300 mg (50 mg every 4 to 6 hours) (Ref. 4).

In another study, Peirce and Mothersill studied 77 patients and reported that five patients receiving treatment with methapyrilene hydrochloride in daily amounts of 100 to 200 mg showed minor side effects but no toxic symptoms (Ref. 5). Rarely did side effects interfere with the patient’s ability to continue the administration of the drug. In some cases, lowering the dosage obviated the side effects without significantly altering the therapeutic effectiveness of the drug. Peirce and Mothersill concluded that ordinarily, 200 mg could be taken daily with “no discomfort” (Ref. 5).

Douglas stated that methapyrilene hydrochloride has been found to have low to intermediate activity for sedation, and its action is less pronounced than that of other antihistamines in therapeutic doses, particularly diphenhydramine (Ref. 3). The anticholinergic action of antihistamines generally may predominate and methapyrilene may cause excitation that results in insomnia, tremors, nervousness, irritability, and palpitation. Dryness of mouth, blurred vision, urinary retention, tachycardia, and constipation may also occur, but these reactions are rare unless large doses are used (Ref. 3). This same view of the toxicity of methapyrilene also appears in several scientific texts (AMA Drug Evaluation, and New and Nonofficial Drugs) (Refs. 6 and 7). However, AMA Drug Evaluation also states that convulsions have been reported with injections of the cerebral cortex and in individuals who have ingested toxic doses (Refs. 6 and 7).

In a study of three patients receiving 400 mg a day for 8 to 10 weeks, no change in blood or urine constituents was observed (Ref. 4). An accidental overdose of 800 mg methapyrilene in a 20-month-old infant resulted in cyanosis, loss of consciousness, convulsions, and cardio-respiratory depression with eventual recovery (Ref. 9). An unusual case of fever, rigor, vomiting, and general toxidromes was reported for methapyrillene hydrochloride (Ref. 4). An accidental overdose of 300 mg resulted in convulsions and coma (Ref. 16). The symptoms recurred after challenge with methapyrilene 2 weeks after the initial attack. An 18-year-old man who became stuporous after ingestion of an unknown quantity of methapyrilene recovered (Ref. 10).

Methapyrilene fatalities have included a 16-month-old girl who developed hyporexia, cerebral edema, upper respiratory tract inflammation, and agitation followed by an adult suicide who died in convulsions after ingestion of methapyrilene (Ref. 12), and two other adults who were found dead (Refs. 13 and 14). None of the fatalities involved children. Four adults and seven others manifested convulsions, and two other adults in coma (Ref. 16).

The Panel has considered the most recent reports compiled from Poison Control Centers during 1973 in which 543 million dosage units of methapyrilene were sold. (See part VII, paragraph A.9, above—Human studies) No fatalities were reported for methapyrilene fumarate or methapyrilene hydrochloride, 11.9 percent exhibited some symptoms and 5.5 percent exhibited symptoms serious enough to require observation at a hospital. There were no fatalities reported with the drug.

The Panel’s review of the data supplied by the Food and Drug Administration continues the data of one adverse reaction report on methapyrilene since 1968 (Ref. 17).

The Panel concludes that methapyrilene fumarate and methapyrilene hydrochloride are safe for OTC use as antihistamines in the dosage ranges described below.

(2) Effectiveness. Tests in animal models have demonstrated methapyrilene’s activity as an antihistamine. Methapyrilene prevents histamine-induced contraction of the guinea pig ileum and protects sensitized guinea pigs from anaphylactic shock when challenged with an antigen (Refs. 2 and 19).

No double-blind human studies using methapyrilene alone were found. Uncontrolled studies of methapyrilene reported that 63 to 79 percent of patients suffering from allergic rhinitis obtained some benefit following administration of the drug (Ref. 9). In the Friedlander study, approximately 75 percent of the 40 patients suffering from acute seasonal allergic rhinitis obtained some benefit from methapyrilene fumarate or methapyrilene hydrochloride, although the relief of the symptoms was seldom complete. This study utilized 100 mg doses in adults administered 4 times daily, symptoms and at bedtime (Ref. 20).

The Peirce and Mothersill study found that 75 patients received methapyrilene hydrochloride for periods varying from 1 day to 3 months (Ref. 4). The study exhibited its greatest effectiveness in acute skin rash due to drug and food allergy, watery eyes and runny nose due to pollen, and/or mild histamine-induced headaches. They found that the effective dosage ranged from 50 to 400 mg daily. The average maintenance dose for all cases was between 150 to 200 mg daily (Ref. 9).

In the Feinberg and Bernstein study of 112 patients with allergic rhinitis (seasonal as well as that due to the pollen of trees, grasses and weeds, and to the spores of molds). 75 percent benefited from methapyrilene hydrochloride. Of 95 patients with vasomotor rhinitis (nonseasonal hay fever) 44 patients or 45 percent received some relief from rhinitis. The symptoms of asthma were not appreciably altered in 30 patients although the pruritic, psammatic, coryza symptoms (Ref. 19). These side effects were helped in 4 of 12 patients. In 13 patients with atopic dermatitis (skin rash), 8 obtained considerable relief from itching. In 12 children with asthma, no benefit was seen.

In addition, the Panel recommends the following specific labeling: (1) Warning, “May cause marked drowsiness.” (2) Professional labeling. The Panel recommends that this labeling be utilized by health professionals, but not to the general public may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.
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histamines, 5-Hydroxytryptamine and An-
Shock of Guinea Pigs."

L. Hicks, Massachusetts, Publishing Sciences Groun, Inc., Acton, Massa-
Antihistamine Drug, the Medical Sciences,
allergic Activity of N-(alpha-pyrldyl) -N-

nymes.

(9) Peirce, J. D. and M. H. Mothers-
"Treatment of Allergic Symptoms with a New

"AMA Drug Evaluations," 2d Ed., Publish-

(20) Feinberg, J. L., and L. F., "Bronchoconstrlcter

(Ref. 4). In a review of clinical studies

(Refs. 7) and 8). In another report, 76.2 percent of 197

15 percent, 25 percent and 10 percent reported no relief, In the

17. The Panel has considered the most recent

data available from the records

"J. Medical Pharmacology,"

"Phenindamine tartrate as an antihistamine in man. A dose of

220 mg of phenindamine inhibited the

and 2). Of the 180 patients in the study

with hay fever who took the drug during the

hay fever season, 44 percent reported complete relief, 22 percent

related relief, 14 percent slight relief and 10 percent reported no relief.

In the 71 patients with allergic perennial rhini-

35 percent had complete relief, 39 percent moderate relief, 9 percent slight

and 17 percent had no relief. The

relief from a dose of 35 mg lasted ap-

approximately 2 to 5 hours. Of the 399 pa-

patients, 23 percent had side reactions such as nervousness, vomiting,

insomnia, drowsiness, head-

ache, constipation, etc. No appreciable

change was seen in blood pressure or

electrocardiogram.

In another report, 76.2 percent of 197

patients with hay fever who were given

given a daily dose of 25 to 150 mg of phenin-

damine for an average of 17 days

reported fair to excellent relief (Ref. 17). The

drug was of benefit to 76.1 percent of the

71 patients with seasonal

vasomotor rhinitis in this study.

The symptomatic relief of allergi-

pharmaceutical and nonpharmaceutical agents used in the treat-

The Panel concludes that phenindami-

tartrate is safe and effective for OTC use as an

antihistamine in suppressing the

symptoms of allergic rhinitis as specified in the
dose section discussed below.

(11) Safety. Acute toxicity studies in guinea

pigs and in rats with intraperitoneal

Injection of 125 mg of phenindamine tartrate is ap-

proximately the same as the intraper-

itoneal LD50 value for diphenhydramine.

Daily dosages of 100 mg of 150 mg or

200 mg or more were reported to have no adverse effects on the weight,
blood formation, blood glucose and non

protein nitrogen of dogs. No histopatho-

logical changes were found (Refs. 1 and 2).

In 136 healthy subjects ingesting 75 to

600 mg phenindamine daily for 7 to 31
days, toxicity studies revealed no abnor-

mality of the blood, blood count or

white cell count, urinalysis, blood pres-

sure, electrocardiogram, gastric acidity,
glucose tolerance, pulse rate, basal meta-

bolic rate or blood chemistry (Ref. 3). In

one study, stimulation is reported

involving persons and drowsiness in others

(Ref. 7). In one study, stimulation was reported to have occurred in 35 percent

of patients (Ref. 4). In a review of clinical studies

(Ref. 7) comprising 250 patients

with allergy, 75 percent reported slight increase in blood pressure, 7 percent

had drowsiness and 12 percent had

stimulation. However, data that

would establish the frequency of stimu-

lation or drowsiness among those taking

the drug in a compassionate dosage

were inadequate and cannot be used for mak-

ing phenindamine an exception with

respect to a warning regarding the

occurrence of drowsiness as a side effect.

The Panel concludes that phenindama-

tartrate is safe for OTC use as an

antihistamine in the dosage ranges
disclosed above.
relief to 18 percent, partial relief to 62 percent and 20 percent were not helped (Ref. 3). Daily doses of 75 to 250 mg to 25 patients with vasomotor rhinitis brought no relief for 44 percent and complete relief for 20 percent. At 75 mg daily, approximately 26 percent of the patients showed side effects.

Experience has also indicated that the duration of action is rapid, occurring within 15 minutes of ingestion (Ref. 1). In one study, 86 percent of 68 patients with hay fever received moderate to complete relief receiving a dosage of 25 to 150 mg daily. In a review of the antihistamine drugs (Ref. 7), 76 percent of 912 patients with allergic rhinitis were benefited.

In one study, moderate to marked relief of hay fever occurred in 78 percent of 40 patients taking 50 mg daily (Ref. 4).

Seventy-eight percent of patients with hay fever noted to fair to excellent relief (Ref. 1). A placebo failed to provide relief of the symptoms in these patients. The Panel concludes that pheniramine tartrate 25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) Dosage. Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 75 mg daily. Children 2 to under 6 years of age need 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(4) Labeling. The Panel recommends the following specific labeling: (1) Warning. "Caution: May cause nervousness and insomnia in some individuals." (2) Professional labeling. The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years of age need 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

REFERENCES


(8) OTG Volume 040285.

g. Pheniramine maleate. The Panel concludes that pheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) Safety. Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity and a low order of toxicity (Refs. 1 and 2). Clinical experience has confirmed that pheniramine maleate is safe in the dosage ranges used as an antihistamine. The chief side effect of pheniramine appears to be sedation. It also appears to have a mild atropine-like effect. Since most of the studies have been conducted with the tartrate form of pheniramine, the action of this drug alone cannot be described with certainty. In one study in which pheniramine alone was given, drowsiness and dryness of the mouth (atropine-like effect) occurred in 11 percent of the subjects (Ref. 3). In a review of clinical studies with the antihistamine drugs (Ref. 4) 20 percent of 40 patients receiving pheniramine maleate 25 mg for allergic rhinitis had side effects, chiefly drowsiness. Among 184 subjects receiving 10 mg pheniramine 4 times daily in the course of a double-blind study of the "common cold," side effects, chiefly drowsiness, did not significantly exceed the side effects in an equal number of subjects receiving a placebo (Ref. 5). There appear to be no reports of accidental overdose. A single case was described in which acute psychosis occurred following treatment for 2 months with pheniramine 25 mg 3 times daily (Ref. 6). Following the withdrawal of pheniramine, recovery occurred in 8 days. No definite conclusion could be drawn in this case as to the role played by pheniramine. An atropine-like effect suggests a potential hazard in patients with enlargement of the prostate gland and also narrow angle glaucoma and this effect also has been considered to be disadvantageous in patients with asthma although data supporting this potentially adverse effect are not available.

The Panel has considered the most recent data from the records compiled from Poison Control Centers during 1973 in which a minimum of 291 million dosage units were sold. (See part VII, paragraph A.6. above—Human toxicity.) Of the 398 suspected poisonings reported for pheniramine maleate, 20 percent exhibited some symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug being identified as a contributing factor of death.

The Panel views the data supplied by the Food and Drug Administration disclosed no adverse reaction to the drug for pheniramine maleate since 1968 (Ref. 7).

The Panel concludes that pheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) Effectiveness. Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity (Ref. 1 and 2).

There are no well-controlled studies documenting the effectiveness of pheniramine maleate as an antihistamine. In a review of several reports of clinical experience, pheniramine in a dose of 25 mg gave relief of allergic rhinitis in 81 percent of 442 patients (Ref. 4). Exercise of the drug gave relief in 65 percent of patients with nonallergic rhinitis (vasomotor rhinitis).

The Panel concludes that pheniramine maleate 12.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) Dosage. Adult oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 75 mg daily. Children 2 to under 6 years of age need 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(4) Labeling. The Panel recommends the following specific labeling: (1) Warning. "May cause marked drowsiness." (2) Professional labeling. The Panel recommends that labeling provided to health professionals, but not to the general public, may contain the following additional dosage information: Children 2 to under 6 years of age need 3.125 to 6.25 mg every 4 to 6 hours not to exceed 15.625 mg in 24 hours.

REFERENCES


(7) Melpolder, A. R. and F. V. Rockwell, "Toxic Deaths Due to Prophenamidine (Trimebut), Report of a Case," The Journal...
Proposed Rules


(7) OTC Volume 040325.

h. Promethazine hydrochloride. The Panel concludes that promethazine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) Safety. Promethazine is well-tolerated by laboratory animals; doses which greatly exceed those giving protection against histamine are well tolerated by guinea pigs (Ref. 1). Like other antihistamine drugs, promethazine may cause drowsiness when taken in clinically effective doses. In a study in which up to 1 gm was administered therapeutically 4 times daily to psychiatric patients, drowsiness occurred as the most important and frequent side effect (Ref. 2). In a suicide attempt a 25-year-old female survived an estimated dose of 1.5 gm, developing coma and clonic contractions (Ref. 3). Another such case had a similar course after the patient consumed 500 mg of promethazine (Ref. 4). Children may be less tolerant of this drug. Seven to 10 hours after an old boy who received 200 mg, he was hospitalized with many symptoms including restlessness, excitation, stupor, fright and hallucinations. Recovery followed in 3 days (Ref. 5).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 385 million dosage units were sold. (See part VII, paragraph A.8. above—Human toxicity.) Of the 66 reported suspected poisonings for promethazine, 26.5 percent exhibited some symptoms and 14.3 percent exhibited symptoms severe enough to require treatment or observation at a hospital. There were no fatalities reported with the drug. This relative incidence of adverse reactions is remarkably low in light of the substantial and long use of the drug (1/2 billion oral doses have been used since 1951 (Ref. 6)).

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 169 adverse reactions involving marketed products containing promethazine (Ref. 7). Of the 169, 4 adverse reactions were considered definitely related to the oral ingestion or injection of promethazine. 105 were listed as probably caused by the drug's use, 49 were listed as possibly related to its use and 11 were listed as unrelated to promethazine.

Of particular concern are blood dyscrasias which have been reported associated with promethazine use. A total of nine adverse reaction reports have remotely related blood dyscrasias to promethazine. Analysis of the experience reports indicates that these dyscrasias are not attributable to promethazine. One case of agranulocytosis is reported to have occurred in a patient who was receiving promethazine and methaqualone. The patient's white count and the neutrophils began to increase and returned to normal 3 days after methaqualone was discontinued. Agranulocytosis was reported in another patient receiving doses of two antihistotics intravenously who was also receiving oral promethazine. Additional drugs in the regimen included a thyroid derivative and tetracycline prior to the other. It is possible that these drugs may well be attributed to the two antihistotics, methacholin and/ or cephalothin, both of which are known to cause agranulocytosis alone. Thrombocytopenia was reported in a 2-year-old child who developed symptoms of an upper respiratory infection with fever and cough. The patient was treated with aspirin, a product containing tripropylene hydrochloride and pseudoephedrin, and promethazine syrup with dextromethorphan. The attending physician believed that the thrombocytopenia was caused by the basic disease process and not by the medication. Leukopenia and thrombocytopenia was reported in a patient receiving promethazine but there are no data provided on the patient's disease state or concomitant drug therapy. On the basis of this limited data it is not possible to determine the cause and effect relationship between promethazine and the blood dyscrasias. Another patient, an 88-year-old male, with an upper respiratory infection who was receiving promethazine, tetracycline and propoxyphene was reported to have had anemia and leukopenia which were secondary to drug reaction. Again, no information on drug dosages or final diagnosis was available and promethazine cannot be determined to cause the hypoplastic anemia.

A further review of adverse reaction reports from the Boston Collaborative Drug Surveillance Program and the University of Florida adverse reaction study shows a low incidence (5.5 percent and 7.1 percent, respectively) of adverse reactions (Ref. 8). The most frequently occurring reactions were drowsiness and confusion or disorientation. In contrast to other phenothiazine derivatives, promethazine showed few incidences of extrapyramidal syndrome (1 of 2,468 patients followed in the studies who received promethazine). Clinical studies (Refs. 1, 9, 10, and 11) indicate that the drug is safe in a dosage effective in allergic rhinitis and authorities in the field of clinical allergy concur (Refs. 12 and 13).

The Panel is aware of the current professional literature on the subject of promethazine which warns against variable possible adverse reactions. These adverse effects are those usually associated with phenothiazine derivatives and clinical experience indicates their occurrence with most other phenothiazine compounds. According to one authority, jaundice, excessive hypotension or hematopoietic damage have not been reported (Ref. 13).

The Panel recommends that labeling provided to health professionals be such as to warn against variable possible adverse reactions. The Panel concludes that promethazine does not cause the wide range of serious or potentially toxic effects characterizing other members of the chemical class of phenothiazines.

It should be noted that while promethazine is currently available only by prescription, the dosage levels are comparable to those that would be available in over-the-counter preparations. The safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that promethazine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) Effectiveness. Promethazine is highly effective in protecting guinea pigs against histamine and the drug is also effective in protecting guinea pigs against anaphylaxis (Ref. 10). Promethazine appears to share with other antihistamine drugs under consideration the capacity to suppress rhinorrhea, sneezing and itching but differs from most other antihistamine drugs under consideration in having a longer duration of action. However, no controlled clinical trials appear to have been done to test the effectiveness of promethazine in allergic rhinitis nor is the "common cold". A number of uncontrolled studies indicate that promethazine is effective in the treatment of allergic rhinitis in a dose of 13.5 to 55 mg per day (Refs. 6, 7, 10, and 18). Based on the published experience and the data available, the Panel concludes that promethazine is effective when taken in the recommended dosage.

The Panel concludes that promethazine hydrochloride 6.25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) Dosage. Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 15.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommendation except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category 2 labeling for antihistamine active ingredients (See part VII, paragraph B.1. below—Category 2 Labeling.) In addition, the Panel recommends the following specific labeling: (1) Warning. "May cause marked drowsiness." (2) Professional labeling. The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.75 mg in 24 hours.

References


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(6) OTC Volume 040319.

(7) OTC Volume 040523.


(11) "Pyrimidine Maleate—The Panel recommends pyrimidine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(12) OTC Volume 040234.


(14) Pyrimidine Maleate. The Panel concludes that pyrimidine maleate is safe and effective for OTC use in suppressing symptoms of allergic rhinitis as specified in the dosage section discussed below.

(15) Safety. Chronic animal toxicity studies done by Winter et al. showed no evidence of a cumulative effect (Ref. 1). In that study, pyrimidine maleate had been administered to rats, dogs and monkeys for varying lengths of time up to 6 months. The following doses appeared to be entirely safe: in rats 10 mg/kg 5 times weekly for 6 months and up to 200 mg/kg daily for 25 days; in dogs; 20 mg/kg 5 times weekly for 6 months, and in monkeys, 50 mg/kg daily for 35 days. No toxic signs or any hemato logical, biochemical or pathological abnormalities were found in the animals on these doses.

In human studies, pyrimidine has a low order of toxicity. Side effects are not infrequent, but are usually mild. They include drowsiness, lightheadedness, dizziness, and anorexia (loss of appetite) (Refs. 2). In a study by Gay et al., only 3 percent of the 147 patients showed any sign of drowsiness and the incidence of loss of appetite, nausea and vomiting occurred in 27 percent of the patients (Ref. 3).

Two fatalities were reported with pyrimidine maleate. One was a 21-month-old child who had ingested 600 mg and died 24 hours after ingestion, exhibiting a post-convulsive coma. The other fatality was of a 2-year-old child that had ingested 1,600 mg and died during convulsions 4 hours after ingestion (Ref. 4).

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 24 adverse reaction reports on pyrimidine since 1968 (Ref. 5). Both of the adverse reactions were minor and neither was listed as directly related or probably caused by the ingestion of pyrimidine.

The Panel has considered the most recent data available from the records compiled by Poison Control Centers. (See part VII, paragraph A.6. above—Human toxicity.) Of the 35 suspected reactions reported for pyrimidine maleate, 18.7 percent exhibited symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of only two adverse reaction reports on pyrimidine since 1958 (Ref. 6). Of the two reports, no adverse reactions were listed as being definitely related to ingestion of pyrimidine; both were listed as possibly related to its ingestion.

The Panel concludes that pyrimidine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) Effectiveness. In vitro and in vivo animal studies indicate that pyrimidine has an intense antihistamine action (Ref. 6) and that the drug has protective activity against histamine-induced anaphylactic reactions in the guinea pig (Ref. 7). Pyrimidine and diphenhydramine were equally effective in protecting against anaphylactic reactions and the prevention of histamine-induced contractions of guinea pig ileum in this same study (Ref. 8). In a dose of 0.1 mg/kg of pyrimidine, 100 percent of 10 guinea pigs pretreated with 0.5 mg/kg of histamine survived. The pharmacological effects and the histamine antagonism of pyrimidine are comparable to those of chlorpheniramine and similar to that of other antihistamines (Refs. 1, 6, and 7).

In an uncontrolled study of several antihistamine drugs including pyrimidine (Ref. 9), this drug was given to 102 patients with allergic rhinitis of whom 70 percent were improved. Two other comparative uncontrolled studies gave similar findings (Refs. 8 and 9) and in a comparative study of antihistamines, 60 percent of 604 patients with allergic rhinitis usually receiving a dose of 50 mg were benefited (Ref. 10).

The Panel concludes that pyrimidine maleate is safe and effective for OTC use in suppressing symptoms of allergic rhinitis as specified in the dosage section discussed below.

(3) Dosage. Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 300 mg in 24 hours. Children 2 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed above and the professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antihistamines. (See part VII, paragraph B.1. below—Category I labeling.) In addition, the Panel recommends the following specific labeling: Promethazine Maleate. The Panel recommends that the labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

REFERENCES


(5) OTC Volume 040253.


1. Thonzylamine hydrochloride. The Panel concludes that thonzylamine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(2) Safety. Thonzylamine hydrochloride has been shown in animal experiments to possess antihistaminic activity and a low order of toxicity (Ref. 1). Clinical experience has confirmed the antihistaminic activity and a low order of toxicity of thonzylamine hydrochloride (Refs. 2 and 3). In one report in which patients with "allergy" received an average dose of 50 to 100 mg per day, 2 out of 7 patients in seven separate studies concurred that...
thonzylamine was the "least toxic" of the antihistamines then in general use (Ref. 4). In other studies, the incidence of side effects was also low (Refs. 5 through 9) but the dosage of thonzylamine was generally selected at levels greater than those in the entire series of 874 patients, an average of 10.9 percent reported side effects which consisted of slight nervousness, headache, gagging, dizziness, and dizziness. Most of these side effects were not significant, but the drug was discontinued in a small number of patients due to headache or gastric disturbance.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 89 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) There were no reported suspected poisonings for thonzylamine hydrochloride.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thonzylamine hydrochloride since 1968 (Ref. 10).

The Panel concludes that thonzylamine hydrochloride is safe for OTC use as an antihistamine at the dosage ranges described below.

(2) Effectiveness. Thonzylamine hydrochloride, administered orally, is generally recognized as possessing antihistamine properties and providing symptomatic relief in allergic rhinitis. However, there are only uncontrolled studies documenting the effectiveness of thonzylamine hydrochloride as an antihistamine.

Most textbooks and several studies (Refs. 5, 7, and 9) indicate thonzylamine hydrochloride has antihistamine action. In a series of uncontrolled studies, 64 percent of patients with "allergy" benefited from oral doses of 50 to 100 mg thonzylamine hydrochloride 2 to 4 times daily (Ref. 4) while in the other studies, thonzylamine was found to be about as effective as other antihistamine drugs. In a review of the antihistamines, thonzylamine 50 mg was reported to have given benefit in 54 percent of 384 patients with allergic rhinitis. (Ref. 11) The studies cited suggest that a recommended dosage of 50 to 100 mg up to 4 times a day is effective.

The Panel concludes that thonzylamine hydrochloride 50 to 100 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) Dosage. Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I Labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: Professional labeling. The Panel recommends that labeling provided to health professionals (but not to the general public) contain the following dosage information: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

REFERENCES

(1) OTC Volume 04033.
(10) OTC Volume 04032.

Category I Labeling

The Panel recommends the following Category I Labeling for antihistamine active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. Indications. (1) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)."
(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)."
(3) "Alleviates, decreases, or for temporary relief of, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)."
(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)."
(5) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)."
(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)."

b. Warnings. The droxiness often produced by the antihistamine drugs is a potential hazard under circumstances in which alertness is important. Therefore, the Panel believes that a warning regarding drowsiness should appear on the label for all products containing antihistamine ingredients. The Panel believes it is prudent to regard the atropine-like effects of the antihistamines as a possible hazard in patients with glaucoma and as possibly leading to difficulty in urination in those individuals with prostatic hypertrophy. In asthma, the antihistamines may cause drying of bronchial secretions, making expectoration of the secretions more difficult and thereby increasing obstruction of the airway.

Therefore, the Panel recommends that labeling include the following warnings and cautions: (1) For active ingredients not containing the specific warning "May cause marked drowsiness," the statement "May cause drowsiness" should be used.
(2) "May cause excitability especially in children."
(3) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician." (4) "Caution: Avoid driving a motor vehicle or operating heavy machinery."
(5) "Caution: Avoid alcohol beverages while taking this product."
(6) "Do not give this product to children under 6 years except under the advice and supervision of a physician."

There are insufficient data to establish the safety of OTC preparations containing antihistamines in children under 6 years. Individuals vary widely in the degree to which drowsiness, and less commonly, other adverse effects occur when they are given antihistamine drugs. For this reason, the frequency and severity of side effects cannot be predicted. Respiration may be depressed and this effect can be serious in infections involving the airway. Parents and others may have difficulty assessing the intensity of induced side effects and children cannot be expected to understand their potential hazards. For these reasons, supervision is recommended when children under 6 years are given antihistamine drugs.

2. Category II conditions under which antihistamine ingredients are not generally recognized as safe and effective or are misbranded. The use of antihistamines under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following labeling should be removed from the market until scientific testing support their use.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is do-

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Studies in humans also suggest a low incidence of side effects at a dosage of 100 to 200 mg in 24 hours with moderate drowsiness occurring following dosage in excess of 200 mg in 24 hours (Ref. 2). One reference states that in these high doses, soporific effects occur in less than 7 percent of patients (Ref. 3). A low incidence of side effects, 6.5 percent, was reported in one study in which allergic patients were given 25 mg, 50 mg, 100 mg, 3 or 4 times daily (Ref. 4). In another study (Ref. 5), phenyltoloxamine was given for its "attractive" effect in a dosage of 200 mg daily, 100 mg after lunch for daytime sedation and 200 mg at bedtime for nighttime sedation. Side effects were reported to be minimal in this study.

The Panel concludes that although there are insufficient data to determine that phenyltoloxamine citrate is effective for the relief of the symptoms of allergic rhinitis, 50 mg is the proposed dosage at which this ingredient is most likely effective.

(3) Proposed dosage. Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 12 years of age are given a dosage of 5 mg every 4 to 6 hours not to exceed 150 mg in 24 hours; children 2 to under 5 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(5) Evaluation. Data to demonstrate effectiveness will be required according to the 1976 guidelines set forth below for testing antihistamine drugs. (See part VII. para.

References


6. The Panel concludes that phenyltoloxamine hydrochloride (oral) is safe for OTC use but there are insufficient data available regarding its effectiveness to permit final classification as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the proposed dosage section discussed above.
classification as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) Safety. Clinical experience has confirmed that thenyldiamine hydrochloride (oral) is safe in the dosage ranges used as an antihistamine. The Panel has discussed the topical use of this drug as a nasal decongestant and has referenced this document. (See part VIII, paragraph B3.k. below—Thenyldiamine hydrochloride (topical.).

This drug was selected from among several related compounds because of marked antihistaminic and anti-anaphylactic properties and its low toxicity in animals (Refs. 1 and 2). Thenyldiamine is relatively nontoxic in animals. The oral LD₅₀ for mice is about 180 mg/kg and for the guinea pig 240 mg/kg. There are no human safety data on the use of thenyldiamine administered orally alone. Data in uncontrolled studies with a combination product containing phenylpropanolamine, acetaminophen and caffeine in addition to thenyldiamine in a dose of 25 to 150 mg/kg did not show significant changes in pulse rate or blood pressure (Refs. 3 and 4). Tabulations of side effects in patients receiving thenyldiamine hydrochloride alone or in combination with the combination formulation are difficult to interpret. The chief side effect appears to be sedation or drowsiness. Dizziness, dryness of the throat, headache, perspiration, and nausea have also been reported (Ref. 1).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers in the U.S. in 1972 in which 2.5 million dosage units were sold. (See part VII, paragraph A.6. above—Human toxicity.) In the one suspected poisoning reported for thenyldiamine hydrochloride, no symptoms were exhibited.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thenyldiamine hydrochloride since 1968 (Ref. 5).

The Panel concludes that thenyldiamine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (oral) as an antihistamine and reports of clinical experience are lacking. Thenyldiamine hydrochloride was official in U.S.P. XII. The dose was 15 mg orally. The frequency of treatment was not stated. A secondary reference source indicates the dosage to be 15 to 30 mg (Ref. 6). It appears that effective adult dosage may be expected to reflect the previously commercialized OTC combination products which contain 2.5 to 7.5 mg per dosage unit.

In vitro studies of 0.03 gamma thenyldiamine in a 20 ml bath gave 75 percent inhibition of a standardized contraction produced by 0.3 gamma histamine. The drug compared well with diphenhydramine and pyrilamine as measured by histamine shock in the guinea pig where 1 mg/kg gave complete protection against the LD₅₀. The drug also gave marked protection against anaphylaxis in the guinea pig.

The Panel concludes that although there are insufficient data to determine that thenyldiamine hydrochloride (oral) is effective for the relief of the symptoms of allergic rhinitis, 15 to 30 mg are the proposed dosage at which this ingredient is most likely effective.

(3) Proposed dosage. Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII, paragraph B1. above—Category I Labeling.) However, the Panel recommends that the Category I warning pertaining to use in children be revised from 6 years to 12 years with the following specific labeling: (i) Warning. "Do not give this product to children under 12 years except under the advice and supervision of a physician." (ii) Professional labeling. The Panel recommends that under professional labeling the patient be referred to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 7.5 mg to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours; children 2 to under 6 years oral dosage is 3.75 mg to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours.

(5) Evaluation. Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII, paragraph C. below—Data Required for Evaluation.)

REFERENCES

(3) OTC Volume 040167.
(4) OTC Volume 040169.
(5) OTC Volume 040325.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antihistamines. Additional data are recommended for these claims for OTC antihistamine use: a. The following statements of duration are unacceptable unless documentation can specify the number of hours: "provides hours of relief" "all day" "all night".

b. "Alleviates, decreases or for temporary relief of running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in the common cold".

c. "Alleviates, decreases or for temporary relief of running nose as may occur in the common cold".

d. "Alleviates, decreases or for temporary relief of sneezing as may occur in the common cold".

e. "Alleviates, decreases or for temporary relief of itching of the nose or throat as may occur in the common cold".

f. "Alleviates, decreases or for temporary relief of itchy and watery eyes as may occur in the common cold".

g. "Dries running nose as may occur in the common cold".

h. Claims that sleep will be facilitated. Terms include "promotes restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a category III product into Category I are in keeping with the present state of the art and do not preclude the use of improvements or improved technology in the future.

1. Principles in the design of an experimental protocol for testing antihistamine drugs in allergic rhinitis. a. General principles. The antihistamine drugs are indicated for the symptomatic relief of IgE mediated allergic reactions. (See part II paragraph B1.—Allergy.) When such reactions occur in the upper airway, the symptoms include sneezing, nasal discharge, nasal obstruction and itching of the nose, eyes, throat and ears. Such symptoms may or may not be accompanied by objective manifestations and for this reason, the patients subjective sensations must be relied upon in the assessment of drug action. However, observations on the degree of edema of the nasal mucous membrane, the quantity of nasal discharge and the degree of injection of the sclerae may be helpful. The action of this group of drugs is limited to a few hours so that repeated doses at regular intervals are required for a sustained effect. All the antihistamines have side effects which again are subjective and have virtually no objective counterpart. Because of the subjective nature of both the symptoms and the effect of any drug-induced change, double-blind experimental control is especially important in the assessment of antihistaminic drugs.

Considerable experience in assessing therapy for allergic rhinitis is found with pollen (hay fever) has accumulated in the past 15 or more years in the course of efforts to determine the effectiveness of injection therapy (immunotherapy). Hitherto unrecognized problems in the selection of cases, the recording and scoring of symptoms, the tally of medication other than preparation(s) under test and the maintenance of experimental control became apparent (Ref. 1).

b. Selection of patients. The selection of patients should be limited to those
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Many of the reports favoring antihistamine use were published some years ago when a well-controlled, randomized, double-blind clinical trial was not generally recognized as important in the evaluation of therapy. How are similar to those of the "common cold" and antihistamines as a group and a placebo identical in appearance and taste to the test drug. In some studies, the patient's state was used to control the patient's condition. Patients who react to one pollen usually react to several other pollens also. Some of the symptoms obtained by skin test may be expected in the patient. If the symptoms are similar to those of the "common cold," this effect must be of a relatively short duration. The results supporting antihistamine use seem not to prevent, abort, or relieve the symptoms of a cold. The general lack of specificity in defining disease and research goals and lack of rigor in research design in manoma and animals are noteworthy. In man, there appears to be little valid evidence that antihistamines have any effect on the common cold.

Studies on the efficacy of the antihistamine drugs in the treatment of the "common cold" may be misleading if the means of selection do not minimize inadvertent inclusion of subjects with allergic rhinitis, the symptoms of which are similar to those of the "common cold." Relief of symptoms will then be erroneously ascribed to effective of the antihistamine drugs on the symptoms of the "common cold" when indeed the observed benefit may be attributable to the known efficacy of the antihistamine drugs in allergic rhinitis. The Panel has earlier discussed in this document both the "common cold" and allergic rhinitis. (See part II, paragraph B.3. above—The "common cold" and part II, paragraph B.6.a. above—Allergic rhinitis.)

The Panel concludes that the effectiveness of the antihistamine drugs in relieving or altering the symptoms of the "common cold" has not been established. If further studies on the effectiveness of the antihistamine drugs are to be carried out, the Panel suggests that particular attention be directed to the selection of subjects and the means of recording symptoms using procedures and methods large enough to give statistically meaningful results.

b. General principles. The symptoms of allergic rhinitis and the "common cold" have many similarities. A watery
nasal discharge is characteristic of allergic rhinitis and is usually in the "common cold" in the first 1 to 3 days. Sneezing is likewise common to both. Iching of the nose and eyes is more common in allergic rhinitis but also occurs in the "common cold." Nasal congestion occurs in both conditions. Coughing is not a frequent symptom of allergic rhinitis but it occurs in a very small percent of cases. Cough likewise occurs in the "common cold," usually in the latter phase of the illness. Fever of low degree may occur in the "common cold," but it is not frequently present. Fever is absent in allergic rhinitis. Watery and redness of the eyes may occur in both conditions (Refs. 3, 4, and 5).

It is commonly stated in texts on allergic disease that examination of the patient with allergic rhinitis reveals swelling within the nose (swollen turbinates) which has a bluish or gray color (Ref. 5), whereas in the "common cold" their color is red (Ref. 4). No studies have been done to test the frequency with which this distinction is diagnostic and its reliability linking the finding of nasal congestion for inclusion in a study of antihistaminic drugs in the treatment of the "common cold" remains uncertain. No other finding on examination appears to be useful in distinguishing between the early phases of the "common cold" and allergic rhinitis.

Because the symptoms of allergic rhinitis and the "common cold" are so similar, the two conditions are readily confused. The reported efficacy of the antihistaminic drugs in the treatment of the "common cold" has been attributed to the inadvertent inclusion of some cases of allergic rhinitis in some studies (Ref. 2) in which condition the antihistaminic drugs are recognized as effective. Unless steps are taken to eliminate subjects with allergic rhinitis from the study population, the results of the study of the "common cold" may be misleading.

c. Selection of patients. Since the distinction between a true allergic rhinitis and the "common cold," especially in its early phases, is difficult or impossible to make on the basis of symptoms and examination, the following means of minimizing inclusion of subjects with symptoms of allergic rhinitis should be adopted:

(1) Subjects giving a history of allergic rhinitis, e.g., hay fever or allergy to animals, should be excluded.

(2) Studies should be done in the months when allergic exposure is less likely and the "common cold" is more prevalent.

Selection of subjects according to these principles alone is not sufficient, for even in a patient with a history of allergy, it is possible that the "common cold" may occur in such a patient. Subjects selected for the studies should be such as to permit determination of each preparation's effect on each type of symptom and the stage in the disease in which this effect is apparent. Therefore, each subject should maintain an appropriate tally of the type, duration and intensity of symptoms. The study should be of sufficient length to encompass the entire illness to determine the effectiveness of the drug under test on the course of the disease. If a subject drops out of the study, the reason for doing so should be determined and recorded.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. Interpretation of data. A recommended dose of the antihistamine should induce a statistically significant reduction in symptoms when compared to the placebo response. Results should be subjected to statistical analysis, a p value of 0.05 or less (95% confidence or more) being acceptable as evidence of a drug effect. A decision on drug effectiveness should be based on demonstrable drug effectiveness in a minimum of three positive comparable double-blind studies based on results from three different investigators or laboratories.

f. Evaluation of safety. If the safety of the drug has not been established, then the effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on symptoms expected to be influenced by the drug. Furthermore, because the antihistamines, the central nervous system is often affected, as indicated by such side effects as drowsiness and fatigue. These should not be regarded as side effects of the drug but as a frequency and intensity that might pose a hazard to the patient in the performance of a daily routine.

REFERENCES


VIII. NASAL DECONGESTANTS

A. GENERAL DISCUSSION

A nasal decongestant is an agent which reduces nasal congestion in patients with acute or chronic rhinitis. These agents may be administered topically as drops, sprays or inhaled vapors or orally in a solid or liquid dosage form. The drug effect is brought about by constriction of dilated blood vessels (vasoconstriction) within the nasal mucosa, thus temporarily reducing the swelling associated with inflammation of the mucous membrane lining the nasal passages.

Topically administered nasal decongestants produce an intense degree of vasoconstriction, a factor responsible for the rapid and pronounced reduction in nasal obstruction. This intense vasoconstriction also accounts for negligible absorption of the nasal decongestant into the general circulation. Consequently, negligible systemic effects occur following topical use of nasal decongestants unless excessive nasal solution is applied causing drainage into the stomach where it may be absorbed. Studies demonstrating minimal systemic absorption of radioactively labeled oxymetazoline following intranasal application (Ref. 2) and negligible cardiovascular effects following normal and excessive intranasal doses of phenylephrine or xylometazoline (Refs. 3 through 7) support this point. Because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is the tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time. Continued and intense drug-induced vasoconstriction can lead to rebound dilatation of the blood vessels as the drug effect subsides. This phenomenon, which intensifies nasal congestion and perpetuates the rhinitis condition, has been termed "rebound congestion." This problem is minimized if topically applied decongestants are administered in accordance with absorb consequent administration intervals for periods not exceeding 3 days.

Another practical caution with the use of topically applied decongestants is in regard to the possible spread of infection if the drug dispenser is used by more than one person. This can occur if the tip of the dropper or spray container comes in contact with the nose during drug administration.

Some of the nasal decongestants (sympathomimetic amines) are also effective when administered orally. Although the intensity of vasoconstriction in the nasal mucosa and associated symptomatic re-
lie of nasal congestion are less than that produced by the topical application of decongestants, the problem of rebound congestion is not a factor with use of the orally administered nasal decongestants. These orally administered sympathomimetic amines are distributed by the circulation to other target tissues as well as to the nasal mucosa and thus produce side effects not seen with following use of nasal decongestants topicaly.

In general, side effects associated with recommended oral doses of OTC nasal decongestants are minimal, and at higher doses may include nervousness, dizziness, and sleeplessness. Individuals with disease conditions which can be aggravated by sympathomimetic drugs, e.g., high blood pressure, heart disease, diabetes mellitus and hyperthyroidism, should not use decongestants orally except under the advice and supervision of a physician. Likewise, patients taking other-drugs whose action can intensify the sympathomimetic drug action, e.g., monoamine oxidase inhibitors, should not take nasal decongestants orally except under the advice and supervision of a physician. The Panel does not feel these restrictions should apply to topically applied nasal decongestants when administered in recommended doses because of their localized action, i.e., minimal systemic absorption.

References

b. Naphazoline hydrochloride (topical). The Panel concludes that naphazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) Safety. Clinical experience has confirmed that naphazoline hydrochloride is safe in the dosage ranges used as nasal decongestants. Having been introduced into China in 1924 (Ref. 6), there has been clinical experience with this drug which is used orally, chiefly from bronchodilatation and usually in a dosage of 25 mg 4 times daily and topically in the nose as a 0.5 percent solution.

(2) Effectiveness. Extensive clinical experience indicates that cephedrine and its salts (topical) are safe in the dosage ranges as nasal decongestants. Rebound congestion would be expected with continued use. However, concentrations of 1 percent or less, as specified by the clinical experience of the Panel, would not be expected to cause this reaction if use is limited to a few days.

b. Naphazoline hydrochloride (topical). The Panel concludes that naphazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) Safety. Clinical experience has confirmed that naphazoline hydrochloride is safe in the dosage ranges used as a nasal decongestant. Studies involving visualization of the nasal mucosa following a single application of naphazoline, 0.05 to 0.1 percent, revealed rebound congestion as a fairly consistent sequel to the 4 to 6 hour period of nasal decongestion (Refs. 1 and 2). The tendency for frequent and continued use due to rebound congestion has been reported by several authors (Refs. 3 through 6). The continued use of naphazoline hydrochloride may result in dependence. To avoid this dependence, naphazoline use should not exceed 3 days duration.

In infants and young children, nasal administration as well as accidental ingestion of 0.05 to 0.1 percent naphazoline have been associated with systemic effects such as sedation, nervousness, increase in systolic blood pressure and bradycardia (Refs. 7 through 13). Furthermore, because rebound congestion with naphazoline is also a problem in infants, this nasal decongestant should probably not be used in children under 6 years (Ref. 1). For children 6 to 12 years, the pediatric concentration of 0.25 percent, should be used to minimize exposure to excess quantities of the drug.

(2) Effectiveness. Single dose applications of naphazoline, 0.1 percent in adult rhinitis patients using objective meas-
urement, revealed onset of nasal decongestion within 10 minutes and persisting up to 6 hours (Ref. 14). A double-blind objective measurement study in children demonstrated nasal decongestion of up to 5 hours duration (Ref. 1). The number and ages of the children and the concentration of naphazoline were not specified. In one study involving repeated administration of 0.05 percent naphazoline drops over a 1-week period, 34 of 35 patients experienced satisfactory nasal decongestion as judged subjectively by the patient and by visualization of the nasal mucosa (Ref. 15).

(2) Dosage. Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 15 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage due to the advice and supervision of a physician.

(3) Dosage. Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 15 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage due to the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII, paragraph B.1. below-Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warnings. (1) For products containing a concentration of less than 0.05 percent naphazoline hydrochloride: "Do not give this product to children under 6 years except under the advice and supervision of a physician." (2) For products containing a concentration of 0.05 percent naphazoline hydrochloride: "For adult use only. Do not give this product to children under 6 years since it may cause sedation if swallowed.

REFERENCES


(16) Nasonmucum Hydrochloride (topical). The Panel concludes that oxymetazoline hydrochloride is safe in the dosage ranges used as a nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) Safety. Clinical experience has confirmed that oxymetazoline hydrochloride is safe in the dosage ranges used as a nasal decongestant. Because the decongestant effect of oxymetazoline hydrochloride-administered as drops or spray persists up to 5 to 6 hours and gradually declines thereafter, rebound congestion after single administration is negligible (Ref. 1). Twice a day dosing which should give adequate relief of nasal congestion should be expected to have a negligible incidence of rebound congestion. Several studies in adults with chronic rhinitis using 0.05 percent oxymetazoline drops or spray for 2 days to 4 weeks support this contention (Refs. 2 through 5).

In one study 92 chronic rhinitis patients used 0.05 percent oxymetazoline spray in both nostrils and 0.025 percent oxymetazoline in the other nostril for 2 weeks. In this double-blind study rebound congestion was subjectively noted in one-third of the oxymetazoline-treated nostrils and two-thirds of the phenylephrine-treated nostrils (Ref. 6). No rebound congestion was noted over a 6 hour observation period following 5 drops of 0.025 percent oxymetazoline in each nostril of 33 children with allergic rhinitis (Ref. 7). In 30 children ages 4 to 10 years with allergic rhinitis, treatment with a 0.025 percent oxymetazoline, 3 drops in each nostril 3 times a day, was associated with no loss of effectiveness during a 2-week treatment period as measured by objective skin irritation and no rebound congestion in 2 weeks posttreatment evaluation period (Ref. 8).

Animal studies with radioactively labeled oxymetazoline indicate that the rate of systemic absorption from nasal application is too slow to achieve pharma-


(9) Summary of Animal Safety Data is included in OTC Volume 49029.

(10) Summary of Human Safety Data is included in OTC Volume 49029.


(12) Phenylephrine hydrochloride (oral/ topical). The Panel concludes that phenylephrine hydrochloride is effective and safe as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) Safety. (i) As an oral nasal decongestant: Clinical experience has confirmed that phenylephrine hydrochloride is safe in the dosage ranges used as an oral nasal decongestant.

Key and Violante reported that oral doses of 40 to 60 mg phenylephrine are necessary for consistent clinically meaningful cardiovascular effects such as increased diastolic pressure and reflex cardiac slowing (Ref. 1). Various reports reinforce the impressions that in normal volunteers, blood pressure and pulse rate responses to 10 to 15 mg oral doses are equal to or only minimally greater than placebo. The maximum blood pressure increase does not exceed 2 to 7 mm Hg and the pulse rate changes do not exceed 1 to 6 beats/min. At doses of 25 mg, blood pressure increases up to 7 mm Hg and pulse rate changes of 13 to 15 min were occasionally noted at some time intervals (Refs. 1 through 11). If patients were also receiving MAOI inhibitors, however, even 10 mg doses of phenylephrine can induce clinically significant cardiovascular responses (Ref. 12).

Overtly perceived side effects at 10-mg doses approximate the incidence and pattern of a placebo response, whereas 15 to 25-mg doses are associated with an increasing incidence of symptoms related to mild central nervous system stimulation (Ref. 1).

(ii) As a topical nasal decongestant: Clinical experience has confirmed that phenylephrine hydrochloride is safe in the dosage ranges used as a topical nasal decongestant. Gummerson, Slambach and Gaines reported a study in which supratherapeutic doses of 0.25 percent phenylephrine-propranololamine 40 mg and pseudoephedrine 40 mg produced a significant decrease in nasal airway resistance persisting for at least 3 hours.

A recent double-blind controlled study involving 50 adult patients with nasal congestion associated with the "common cold" (25 patients in each group) demonstrated that a single oral 10 mg dose of phenylephrine led to a reduction in nasal airway resistance average 53 percent at 15 minutes, 21 percent at 30 minutes, 28 percent at 60 minutes and 26 percent at 120 minutes (Ref. 26). These reductions were all significantly different from placebo at the earliest observation times. These 50 patients were part of a 200-patient subjective evaluation study group with nasal congestion associated with the "common cold". 100 of each who received either 10 mg phenylephrine or placebo at 4-hour intervals over a 12-hour period. Patient subjective evaluation revealed that the phenylephrine 10 mg dose was significantly different from that reported by the placebo group (Ref. 26).

(ii) As a topical nasal decongestant: In a double-blind crossover placebo-controlled study, phenylephrine was given as a 0.5 percent spray. 10 mg in 24 hours repeated in 3 minutes, to one group of 16 patients with head cold and one group of 9 patients with allergic rhinitis. Objective measurements using posterior electronic rhinometry and body plethysmography revealed significant nasal decongestion at the 30- and 60-minute recording times (Ref. 27).

In another study using 0.5 percent phenylephrine spray in 12 adult rhinitis patients, objectively measured nasal decongestant effects persisted from 1 to 3 hours following administration (Ref. 14). In a 2-week subjective evaluation study of phenylephrine 0.25 percent spray in 82 chronic rhinitis patients, the duration of effect following each dose was generally reported to be 4 hours or less (Ref. 18).

(3) Dosage. (i) As an oral nasal decongestant: Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) As a topical nasal decongestant: Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there...
is no recommended dosage except under the advice and supervision of a physician. (4) Local effects: The Panel concludes that the category I labeling for nasal decongestant active ingredients. (See Part VIII, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warnings: (a) For products containing a concentration of 0.125 percent phenylephrine hydrochloride: "Do not give this product to children under 2 years except under the advice and supervision of a physician." (b) For products containing a concentration of 0.25 percent phenylephrine hydrochloride: "Do not give this product to children under 6 years except under the advice and supervision of a physician." (c) For products containing a concentration of 0.5 percent phenylephrine hydrochloride: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician." REFERENCES (1) Keys, A. and A. Violante, "The Cardiovascular Effects in Man of Neo-Synephrine (1-alpha-hydroxy - beta - methylamino - 3 - hydroxy-styphylidinedihydrochloride)." Journal of Clinical Investigation, 21:11-15, 1942. (2) Memo to Bird, J. G. from H. Stander, "Analysis of Blood Pressure and Pulse Results from Subjects Given Placebo, Neo-Synephrine*, and Phenylpropanolamine, Orally," is included in OTC Volume 040298. (3) Memo to Luduena, F. from H. Stander, "EP 14. Analysis of Blood Pressure and Pulse Results From Subjects Given Placebo and Neo-Synephrine*, and Orally"," is included in OTC Volume 040298. (4) Memo to Hulme from J. G. Bird, "Neo-Synephrine Oral-In-House Pulse and Blood Pressure Study," is included in OTC Volume 040298. (5) Memo to Lands from F. P. Luduena, "Comparative Study of the Effects of Neo-Synephrine HCL and Propadine HCL on Nasal Air Resting Pressure, Hyaluronide, and Pulse Rate of Volunteers," is included in OTC Volume 040298. (6) Memo to Stuter from N. A. Hulme, "Nasal Decongestant Study by Elizabeth Biochemical Laboratories No. 1," is included in OTC Volume 040298. (7) Memo to Hulme, N. A. from H. Stander, "Neo-Synephrine Oral Study—Elizabeth Biochemical Laboratories No. 2," is included in OTC Volume 040298. (8) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Elizabeth Biochemical Study No. 3," is included in OTC Volume 040298. (9) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Elizabeth Biochemical Laboratory Study No. 4," is included in OTC Volume 040298. (10) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Elizabeth Biochemical Laboratory Study No. 5," is included in OTC Volume 040298. (11) McLaurin, J. W., W. F. Shipman and R. Rosedale, Jr., "Oral Decongestants. A Double-Blind Comparison Study of the Effectiveness of Benzedrine Drugs: Objective and Subjective," Laryngoscope, 71: 64-67, 1961. (12) Ellis, J. D., D. L. Laurence, H. Mattei and B. R. McCrae, "A Study of Monamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure," British Medical Journal, 2: 551-553, 1957. (13) Gundrum, L. K., U. A. Stambuck and J. W. Carnes, "Chloristoma of the Nasion," A.M.A. Archives of Otologyngy, 59: 247-248, 1954. (14) Connell, J. T., "Effectiveness of Topical Nasal Decongestants," Annals of Allergy, 27: 414-425, 1966. (15) Harris, E. H., "Comparative Study of Decongestive Effectiveness of Oxymetazoline Hydrochloride, Phenylpropanolamine, Orally," and Phenylproprine in Asthmatic Children with Hypertension," The Eye, Ear, Nose and Throat Digest, 41: 41-43, 1967. (16) Green, M., "Double-Blind Study of Nasal Decongestion with Oxymetazoline and Phenylproprine in Asthmatic Children with Rhinitis."," Review of Allergy, 29: 862-863, 1963. (17) Van Alyea, O. E. and W. F. Hulme, "Systemic Effects of Intranasal Medication," The Eye, Ear, Nose and Throat Monthly, 31: 478-480, 1952. (18) Van Alyea, O. E. and W. F. Hulme, "Oral Neo-Synephrine—Huntingdon Research Center Study No. 1," is included in OTC Volume 040298. (19) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Huntingdon Research Center Study No. 2," is included in OTC Volume 040298. (20) Memo to Hulme from N. A. Hulme, "Oral Neo-Synephrine—Huntingdon Research Center Study No. 1," is included in OTC Volume 040298. (21) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Huntingdon Research Center Study No. 2," is included in OTC Volume 040298. (22) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Cintex Laboratories Study No. 1," is included in OTC Volume 040298. (23) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Cintex Laboratories Study No. 2," is included in OTC Volume 040298. (24) Memo to Blackmore from N. A. Hulme, "Oral Neo-Synephrine—Cintex Laboratories Study No. 3," is included in OTC Volume 040298. (25) Rodgers, J. M., B. B. Reilly and H. A. Bickerman, "Pharmacologic and Physiologic Studies on Nasal Airway Resistance," Clinical Pharmacology and Therapeutics, 14: 146, 1973. (26) OtCOR Volume 040298. (27) Gould, W. J., "Clinical Summary, NYSC Study MD 50-66." Draft of unpublished data is included in OTC Volume 040298. c. Phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, phenylpropanolamine maleate) (oral). The Panel concludes that phenylpropanolamine and its salts are safe and effective as nasal decongestants for OTC use as described in the dosage section discussed below. (1) Safety. Clinical experience has confirmed that phenylpropanolamine and its salts (oral) are safe in the dosage range used as nasal decongestants. Phenylpropanolamine is one of the most frequently used nasal decongestants, similar in action to ephedrine but with less central nervous system stimulation (Ref. 1). Subjective evaluation studies reveal that, in adults, phenylpropanolamine in plain capsules in doses up to 50 mg every 3 hours is associated with only side effects either equal to or only slightly exceeding those of placebo. The side effects consist of nervousness, insomnia, motor restlessness and nausea (Refs 2 and 3). Boyer reported three patients with prostate hypertrophy who complained of urinary retention for 4 days during dosing but had no urinary retention at effective nasal decongestant doses of phenylpropanolamine (Ref. 3). In three reports involving a total of over 200 children ages 2 to 16, phenylpropanolamine was used in combination with acetaminophen and in one study also with phenyltoloxamomine, was subjectively observed to relieve symptoms of nasal congestion with a low incidence of side effects (Refs 4 through 6). Individuals with normal blood pressure receiving phenylpropanolamine alone, either as a 5 mg plain capsule 4 times daily or as a 50 mg sustained release capsule 2 times daily had no significant effect on blood pressure or pulse rate. No adverse effect on cardiovascular systems was noted after 24 hours of treatment (Refs 7 through 10). Intravenous administration of phenylpropanolamine induced dose-related systolic blood pressure increases in human volunteers, an 16 to 24 mm increase following 20 to 25 mg and a 41 to 82 mm increase following 50 mg were observed (Ref. 11). Phenylpropanolamine 50 mg, in sustained release combination with belladonna alkaloids 0.2 mg, and chlorpheniramine 4 mg, was administered 2 times daily for 7 days to groups of patients with normal anterior chamber angle, with narrow angle but no glaucoma signs and to patients with frank glaucoma controlled by medication. No drug-induced alteration of intraocular tension was evidenced in any of the 2 groups of subjects (Refs. 12 and 13). There have been isolated "letter to the editor" reports of individuals consuming therapeutic doses of phenylpropanolamine-containing preparations and experiencing an acute hypertensive episode (Ref. 14). Details relative to other contributing factors are usually too vague to determine if the phenylpropanolamine was entirely responsible. One "letter" reported an acute overdose of a sustained release phenylpropanolamine combination product, eight capsules containing 50 mg of phenylpropanolamine in combination with isopropamide and diphenylbutyramide, was followed within 3 hours by an acute hypertensive response headache, restlessness and vomiting (Ref. 15). One paper cited three cases of "psychotic episodes" associated with presumably therapeutic doses of phenylpropanolamine 50 mg. In combination with isopropamide and phenyltoloxamomine (Ref. 16). The authors indicated that personality changes following phenylpropanolamine preparations were not an uncommon occurrence in patients in their hospitals. In summary then, at therapeutic doses of phenylpropanolamine taken orally, the incidence of side effects in adults and...
children is low. There have been isolated reports, however, of individuals experiencing idiosyncratic reactions of central nervous system stimulation and/or blood pressure rise following therapeutic doses. These effects would also be expected in most individuals with acute overdoses of the drug.

Prior MAO inhibitor treatment has been clearly shown to potentiate dangerously the blood pressure elevating effect of pheynylpropanolamine (Ref. 17 through 20). A single incident was reported of pheynylpropanolamine 50 mg, in combination with chlorpheniramine and iso-proppamide, antagonizing the antihypertensive effect of bendithidine sulfate (Ref. 21). The antihypertensive effect of gualendine can be antagonized perhaps with bendithidine and chlorpheniramine. Pheynylpropanolamine 40 mg orally induces a peak effect up to 3 hours with gradual return toward control thereafter (Refs. 29 and 30). This investigator also demonstrated that a timed-release formulation of phenylpropanolamine hydrochloride 50 mg in combination with bendithidine alaide 0.2 mg and chlorpheniramine maleate 4 mg induced a significant decrease in nasal resistance compared to placebo over a 10-hour testing interval (Ref. 31).

(3) Dosage. Dosages are based on the phenylpropanolamine hydrochloride equivalent. Adult oral dosage is 25 mg every 4 hours or less not to exceed 150 mg in 24 hours. Children 6 to 12 years oral dosage is 12.5 mg every 4 hours or not to exceed 75 mg in 24 hours. Children 2 to 6 years oral dosage is 6.25 mg every 4 hours or 12.5 mg every 8 hours not to exceed 37.5 mg in 24 hours. Children under 2 years, however, there is no recommended dosage except under the advice and surveillance of a physician.

(4) Labelling. The Panel recommends the Category I label for nasal decongestant active ingredients. (See part VIII paragraph B. 1. below.—Category I Labelling.)

REFERENCES

(12) "Summary of Dr. Muburger’s Study with Contac," is included in OTC Volume 040289.
(13) Memo to Richards, M. Free, "Dr. McCalis Intraocular Tension Study with Contac," is included in OTC Volume 040289.
(18) Mittge, J. R. and R. H. McDonald, "Anaglogism of Hypotensive Action of Chlorpheniramine Maleate in Children under 12 years of age: There is no recommended dosage except under the advice and surveillance of a physician.

(19) Labelling. The Panel recommends the Category I label for nasal decongestant active ingredients. (See part VIII paragraph B. 1. below.—Category I Labelling.)

REFERENCES

(12) "Summary of Dr. Muburger’s Study with Contac," is included in OTC Volume 040289.
(13) Memo to Richards, M. Free, "Dr. McCalis Intraocular Tension Study with Contac," is included in OTC Volume 040289.
(18) Mittge, J. R. and R. H. McDonald, "Anaglogism of Hypotensive Action of Chlorpheniramine Maleate in Children under 12 years of age: There is no recommended dosage except under the advice and surveillance of a physician.

(19) Labelling. The Panel recommends the Category I label for nasal decongestant active ingredients. (See part VIII paragraph B. 1. below.—Category I Labelling.)

REFERENCES

PROPOSED RULES

1. Propylhexedrine (inhalant). The Panel concludes that propylhexedrine (inhalant) is safe and effective as an inhalant nasal decongestant in the dosage range specified as the dosage section discussed below.

(1) Safety. Clinical experience has confirmed that propylhexedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant. Because of a wide margin of safety and the relative freedom from toxic effects, use by inhalation is not contraindicated for patients in whom an ephedrine-like pressor or stimulant action would be undesirable (Ref. 1). Excessive doses, at least six inhalations per nostril, of propylhexedrine inhaler produced no undesirable side effects such as angina attacks, ECG changes, or vasopressor responses in 20 patients with history of severe angina pectoris due to arteriosclerosis (Ref. 2).

Two inhalations of propylhexedrine inhaler, 250 mg per inhaler, is reported to deliver approximately 0.5 mg of the volatile amine (Ref. 3).

Oral doses of propylhexedrine alone, 100 mg, in normal adults induces a 17 to 23 mm blood pressure rise and reflex bradycardia but no overt symptoms of euphoria, hallucinations or dry mouth (Ref. 4). Another investigator reported that 250 mg by mouth induced only slight nervousness, anxiety and tachycardia (Ref. 5). A 3- year old who ingested 18 tablets of propylhexedrine, a total dose of 375 mg, developed pronounced symptoms of central nervous stimulation consisting of insomnia, tremor, muscular hyperactivity and tachycardia (Ref. 6). A 9- year old who ingested 10 tablets of propylhexedrine, a total dose of 375 mg, developed pronounced symptoms of central nervous stimulation consisting of insomnia, tremor, muscular hyperactivity and tachycardia which subsided in 3 days (Ref. -6). This study supports that propylhexedrine is marketed outside of the United States as an anorectic.

One individual ingesting the contents of a propylhexedrine inhaler containing 250 mg of amine plus menthol and lavender oil, developed an extreme illness consisting of central nervous stimulation consisting of insomnia, tremor, muscular hyperactivity and tachycardia which subsided in 3 days (Ref. 7).

(2) Dosage. Adults and children 6 to 12 years of age should receive one inhaler, each containing 0.5 mg of amine per dose, to be inhaled by the nostril. This dose, repeated every 4 hours, provides adequate therapy and is less likely to cause rebound congestion than higher doses (Ref. 8).

In a study of cardiovascular effects, dose responses in four subjects showed that 210 to 240 mg or 3.0 to 3.4 mg/kg were required to raise diastolic blood pressure to 80 mm Hg or above (Ref. 9). Acute blood pressure rises may occur, however if pseudoephedrine in therapeutic doses is taken with MAO inhibitors (Refs. 3 and 4).

(3) Effectiveness. A double-blind subjective study in allergic rhinitis patients showed pseudoephedrine to be better than placebo (Ref. 10). In children, a double-blind subjective study showed pseudoephedrine to be better than placebo in allergic respiratory disease and possibly also in non-allergic respiratory conditions, but no statistics are given (Ref. 9).

In a study of 85 patients, there were no differences between the drug and placebo group subjectively or by rhinometry (Ref. 6). However, significant increases in na-
sial flow rates up to 20 percent after 60 mg orally and lasting at least 2 hours.

Recent work with measurements of nasal airway resistance confirms a nasal decongestant effect after an oral dose of 60 mg lasting up to 4 hours and returning to control values by 6 hours (Ref. 9).

(3) Dosage. Adult topical dosage is 60 mg every 4 hours not to exceed a maximum of 350 mg in 24 hours. Children 6 to under 12 years topical dosage is 30 mg every 4 hours not to exceed 150 mg in 24 hours. Children under 6 years topical dosage is 15 mg every 4 hours not to exceed 75 mg in 24 hours. For children under 3 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling).

REFERENCES


(6) Xylometazoline hydrochloride (topical) The Panel concludes that xylometazoline is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(7) Xylometazoline hydrochloride (topical) Clinical experience has confirmed that xylometazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Because the 'decongestant' effect of xylometazoline hydrochloride, administered as drops or sprays, persists up to 5 hours with gradual decline thereafter, objective measurement studies in adults revealed no rebound congestion after single topical applications of 0.05 or 0.1 percent solutions (Refs. 1 through 4). Both objective and subjective measurement studies of 0.05 percent xylometazoline in infants and children, reveal negligible rebound congestion with 3 times daily dosing for periods of 2 days to 2 weeks (Refs. 5 through 9).


accompanied by a specific time period expressed in minutes or hours, as appropriate.

(12) For products used as topical nasal decongestants with claims for rapid onset of action: Statements relating to time to onset of action such as, "fast" or "quick", must be accompanied by a specific time period expressed in minutes.

(13) For topical nasal decongestants which can demonstrate a cooling sensation: (i) "Provides cooling sensation".

(ii) "Cooling".

(iii) "Cools nasal passages".

b. Warnings. (1) For products used as topical nasal decongestants: (i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge".

(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician".

(iii) "The use of this dispenser by more than one person may spread infection".

(2) For products used as oral nasal decongestants: (i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur".

(ii) "If symptoms do not improve within 7 days or are accompanied by high fever consult a physician".

(iii) "Do not take this product if you have high blood pressure, heart disease, diabetes or thyroid disease except under the advice and supervision of a physician".

(iv) "Drug interaction precaution: Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician".

(3) For products used as inhalant nasal decongestants: (i) "This inhaler should be warmed in the hand before use to increase effectiveness".

(ii) "Do not give this product to children under 6 months of age for oral use except under the advice and supervision of a physician".

(iii) "Children should not have unsupervised access to this inhaler".

(iv) "Caution: Not for use by mouth".

2. Category II Conditions under which nasal decongestant ingredients are not generally recognized as safe and effective or are misbranded. The use of nasal decongestants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following active ingredients and labeling should be removed from the market until scientific testing supports its use.

Category II Active Ingredients

The Panel has classified the following nasal decongestant active ingredients as not generally recognized as safe and effective or as misbranded:

- Mustard oil (allylisothiocyanate) (topical/inhalant)
- Turpentine oil (spirits of turpentine) (oral)
an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as a nasal decongestant. (See part VIII paragraph 23.3.m. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) Effectiveness. Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as a nasal decongestant when taken orally.

(3) Evaluation. The Panel is unable to determine a safe oral dosage for turpentine oil for use as a nasal decongestant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as a nasal decongestant.

REFERENCES


Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling. (See part II, paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the examples of language expressed in the following misleading claims are excessive and claims or claims which do not occur and therefore such labeling should be removed from the market until scientific testing supports their use.

a. Topical nasal decongestants. (1) Reference to "germ-laden mucous" is unacceptable because it implies a curative action rather than symptom-relieving.

b. Oral decongestants. (1) Reference to "fast" or "prompt" onset of relief is unacceptable for oral products because this action does not occur and is a claim allowed only for topical products.

c. Topical or oral nasal decongestants. (1) Reference to effect on "local congestion" is unacceptable because they suggest the product is particularly effective. All Category I ingredients have been judged effective but no acceptable controlled studies were submitted to the Panel documenting one preparation as more effective than another.

(2) Reference to "used by" or "most recommended by doctors or scientists" is unacceptable because it is difficult to substantiate.

(4) "Checks irritation caused by cold virus" is unacceptable because it implies a curative action rather than symptom-relieving.

3. Category III conditions for which the available data are insufficient to permit final classification at this time. The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed. The Panel believes it is reasonable to 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the conditions listed in this category should no longer be marketed in over-the-counter nasal decongestant products. Effectiveness as a nasal decongestant must be demonstrated by determining the ability of a drug to reduce nasal obstruction in patients with acute or chronic rhinitis.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed nasal decongestant active ingredients:

Beechwood creosote

Borinyl acetate (topical)

Camphor (topical/inhalant)

Cedar leaf oil (topical)

1-Desoxyephedrine (Inhalant)

Ephedrine preparations (oral) : Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racedephrine hydrochloride.

Eucalyptol/eucalyptus oil (topical/inhalant)

Menthol/peppermint oil (topical/inhalant)

Phenypropolineamine hydrochloride (topical)

Thymol (Inhalant)

Turpentine (spirits of turpentine) (topical/inhalant)

a. Beechwood creosote. The Panel concludes that beechwood creosote is safe and is effective in such low doses. The Panel believes that it is reasonable to 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the conditions listed in this category should no longer be marketed in over-the-counter nasal decongestant products. Effectiveness as a nasal decongestant must be demonstrated by determining the ability of a drug to reduce nasal obstruction in patients with acute or chronic rhinitis.

(1) Safety. Clinical experience has confirmed that beechwood creosote is in the usual dosages contained in lozenges or cough mixtures for nasal decongestant activity is safe.

(2) Efficacy. Except for a recent submission (Ref. 4), there have been no well-controlled studies documenting the effectiveness of beechwood creosote alone or in combination as a nasal decongestant. A single study is reported dealing with nasal airway resistance in 66 patients with degrees of the "common cold." These patients were studied by objective techniques and showed significant reduction in nasal resistance for beechwood creosote combination as compared with a placebo 2 hours following administration. Subjective studies with respect to runny nose should note significant changes from the placebo. It is stated that the investigator global evaluations were too small in number to permit statistical interpretation. In reviewing this study it is difficult for the Panel to interpret these statistical analyses which appear to be cumbersome and confusing. In addition, since no dosage information is supplied, the Panel questions the acceptability of the study.

According to the standard compendia (Refs. 1 and 5), an average dosage of beechwood creosote is 250 mg 3 or 4 times daily. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Refs. 0). This 48- to 80-fold difference (3.29 mg/lozenge, 2 doses/day) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) Proposed dosage. Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part IV, paragraph B.1. above—Category I Labeling).

(5) Evaluation. Data to demonstrate effectiveness in this category must be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part IV, para-
graph C below—Data Required for Evaluation.

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REFERENCES

(4) OTC Volume 040065.
(6) OTC Volume 040020 and 040035.

b. Bornyl acetate (topical). The Panel concludes that bornyl acetate is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) Safety. Clinical experience has apparently confirmed that bornyl acetate (topical) is safe in the dosage ranges used as a nasal decongestant. There are no studies to substantiate its safety. The Merck Index (Ref. 1) states that this compound may cause nausea and vomiting, mental confusion, dizziness and convulsions. The dose is not given. The amount present in a commercially available inhaler is not given (Ref. 2). It is one of several aromatic substances in the inhaler.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of bornyl acetate (topical) as a nasal decongestant. In a report (Ref. 3), bornyl acetate was one of eleven aromatic substances evaluated as nasal decongestants. Patients presumably with nasal congestion were used. Nasal resistance was measured before treatment and at 5, 15, 30, 60, 90 and 120 minutes after treatment. Bornyl acetate 112.5 mg was impregnated on a cotton wick through which air was forced and the patient inhaled. In the morning, 50 cc of air was administered and 150 cc in each nostril in the afternoon. In 11 patients, there was a statistically significant decrease in the nasal resistance at the higher dose. This was not a well-designed study.

(3) Proposed dosage. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer’s marketed product(s).

(4) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII, paragraph B.1. above—Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

REFERENCES

(2) c. Camphor (topical/inhalant). The Panel concludes that camphor is safe in the dosage ranges used as a nasal decongestant.

(1) Safety. Clinical experience has confirmed that camphor is safe in the dosage ranges used as a nasal decongestant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Inhalation of camphor generally produces toxic effects in adults although up to 0.75 gm of camphor equivalent to a teaspoonful of liniment of camphor or camphorated oil which contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning label is present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with no ill effects. Camphor has a mild local anesthetic action in larger doses it is irritating and can produce toxic effects in the respiratory tract. Taken orally it is safe in the dosage ranges used as a nasal decongestant.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as a nasal decongestant.

The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical/inhalant OTC use as a nasal decongestant.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the face, chest and back. Applications may be repeated up to 3 times daily.

(ii) For topical use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in any hot steam vaporizer, bowl or washbasin; or 2 teaspoonsful of solution per pint of water are added to an open container of boiling water. Breathe in the vapor during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 0.75 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour. For children under 3 years, there is no recommendation for topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for topical nasal decongestant active ingredients. (See part VIII, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning “For external use only. Do not take by mouth or place in nostrils”.

(ii) For steam inhalation use: Warning “For steam inhalation only. Do not take by mouth”.

(5) Evaluation. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(Refs. 4 through 6) and in steam inhalations (Ref. 7). In these studies, although significant nasal decongestion compared to placebo has been demonstrated, it is not evident whether the camphor component contributed to this effect.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the face, chest and back. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in any hot steam vaporizer, bowl or washbasin; or 2 teaspoonsful of solution per pint of water are added to an open container of boiling water. Breathe in the vapor during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 0.75 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour. For children under 3 years, there is no recommendation for topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for topical nasal decongestant active ingredients. (See part VIII, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning “For external use only. Do not take by mouth or place in nostrils”.

(ii) For steam inhalation use: Warning “For steam inhalation only. Do not take by mouth”.

(5) Evaluation. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(Refs. 4 through 6) and in steam inhalations (Ref. 7). In these studies, although significant nasal decongestion compared to placebo has been demonstrated, it is not evident whether the camphor component contributed to this effect.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the face, chest and back. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in any hot steam vaporizer, bowl or washbasin; or 2 teaspoonsful of solution per pint of water are added to an open container of boiling water. Breathe in the vapor during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 0.75 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour. For children under 3 years, there is no recommendation for topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for topical nasal decongestant active ingredients. (See part VIII, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning “For external use only. Do not take by mouth or place in nostrils”.

(ii) For steam inhalation use: Warning “For steam inhalation only. Do not take by mouth”.

(5) Evaluation. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(Refs. 4 through 6) and in steam inhalations (Ref. 7). In these studies, although significant nasal decongestion compared to placebo has been demonstrated, it is not evident whether the camphor component contributed to this effect.
(4) OTC Volume 040298.

**PROPOSED RULES**

**References**

(3) OTC Volume 040297.

## cedar leaf oil (topical)##

**Safety.** Clinical experience has confirmed that cedar leaf oil (topical) is safe in the dosage ranges used as a nasal decongestant.

Cedar leaf oil is the volatile oil steam distilled from the fresh leaves of Thuja occidentalis. The oil is reputed to be both and absorptions cannot be induced with safe doses. The action is like turpentine but the toxicity greater. In most cases of ingestion of a teaspoonful may cause illness in an adult and less than 1 oz may be lethal (Refs. 1 and 2).

Several studies support the safety of a topically applied mixture of volatile oils, 10 percent weight/weight, in petrolatum. Although this mixture contains cedar leaf oil, the concentration of individual ingredients is not specified (Ref. 3).

**Effectiveness.** There are no well-controlled studies documenting the effectiveness of cedar leaf oil (topical) as a nasal decongestant. Cedar leaf oil by inhalation is probably transiently effective as a nasal decongestant.

In a study of 10 patients with head colds, not double-blind or placebo-controlled, inhalation of a measured volume of cedar leaf oil vapor induced a significant nasal decongestant effect lasting for 30 minutes as measured by anterior rhinometry. Increasing the volume of inhaled volatile commercial Cedar oil did not prolong the decrease in nasal resistance (Ref. 4).

In a placebo-controlled crossover study of 26 patients with head colds, application of a 5 percent weight/weight mixture of volatile oils in petrolatum containing cedar leaf oil demonstrated an apparently significant decrease in nasal resistance compared to the petrolatum control over a 4 hour observation period. The concentration of the cedar leaf oil was not specified. A similar study in 20 additional patients resulted in an increase in nasal resistance with overlapping standard errors (Ref. 4).

Other studies involving the objective measurement of nasal decongestant activity of cedar leaf oil utilized mixed nasal decongestant preparations containing camphor, menthol, and other ingredients. In one study (Ref. 5) the decongestant activity of cedar leaf oil was determined in 10 patients with nasal obstruction. Over 3 days, an improvement in rhinoscopic parameters was shown for camphor, menthol and borneyl acetate (Ref. 7).

**Proposed dosage.** The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

**Labeling.** The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII, paragraph B.1. above—Category I Labeling).

**Evaluation.** Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation).

**Proposed Dosage.**

1. Inhalant. The Panel concludes that 1-deoxyephedrine is safe in the dosage ranges used as an inhalant but there are insufficient data to permit final classification of its effectiveness for inhalant OTC use as a nasal decongestant.

2. Topical. The Panel concludes that 1-deoxyephedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant. Application of a 1 percent solution and aqueous spray in concentrations up to 1 percent caused burning, stinging, rhinorrhea and sneezing in up to 21.5 percent of subjects. Epistaxis were rare (Ref. 1). With prolonged use, 25 mg 3 times daily for several days, subjects had transient dizziness and nervousness but no blood pressure changes were noted (Ref. 2). No untoward effects of an oral dose of 25 mg 3 times daily for 1 day were observed in eight patients (Ref. 2).

3. Effectiveness. There are no well-controlled studies documenting the effectiveness of cedar leaf oil (topical) as a nasal decongestant. The effectiveness is therefore uncertain, as data are conflicting and properly controlled objective studies have not been presented.

Uncontrolled studies using nasal drops, 0.25 percent to 1.0 percent concentration, suggest that nasal mucous membrane constriction does occur at the higher concentrations (Ref. 1). An uncontrolled subjective study using an inhaler in 100 patients showed relief of nasal obstruction in 69 percent of cases. Onset of relief was usually 1 minute and lasted up to 4 hours (Ref. 3). In another similar study duration of relief varied from 1 to 2 hours (Ref. 4). Two double-blind studies of inhalers containing aromatic oils and without 1-deoxyephedrine showed no differences in nasal airflow studies using the Butler-Ivy technique (Refs. 5 and 6). However, one study (Ref. 6) showed that the inhalers with or without 1-deoxyephedrine were more effective than a placebo inhaler. This suggests the possibility that at least part of the effectiveness of the inhaler might be due to the aromatic oils. Some improvement for less than 30 minutes in airway resistance was shown for camphor, menthol, and borneyl acetate (Ref. 7).

Two single-blind studies comparing an inhaler containing aromatic oils and 1-deoxyephedrine, an inhaler containing only 1-deoxyephedrine, and a placebo inhaler were done using nasal airway resistance measured by a rhinorrometer (Refs. 8 and 9). Both studies showed that the inhaler with aromatic oils and 1-deoxyephedrine was better than the inhaler containing only 1-deoxyephedrine and both were better than placebo. Activity was maintained for at least 30 minutes with a maximum at 5 minutes but for less than 60 minutes. These studies suggest that 1-deoxyephedrine has some transient nasal vasoconstricor effect.

In a recent double-blind, noncrossover, subjective rhinocscopic study of 100 male patients both the drug containing inhaler and placebo inhaler gave significant subjective effect for up to 60 minutes (Ref. 10). Slight rhinocoscopic improvement was present in both groups. However, the drug containing inhaler groups, when compared with placebo had significantly greater subjective relief and greater improvement in rhinocoscopic parameters.

The above review suggests that 1-deoxyephedrine probably has a vasoconstricor effect which is relatively brief. However, to be certain of effectiveness, double-blind studies with objective measurements of nasal airways of nasal appearance are required. These studies should also provide information as to rebound congestion with repeated nasal use.
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(3) Proposed dosage. Adult inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcg 1-desoxyephedrine is 2 inhalations in each nostril not more frequently than every 2 hours. Children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcg 1-desoxyephedrine is 1 inhalation in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients (see part VIII. paragraph B.1. above—Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required from one additional objective nasal airway resistance study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

References

2. Eudroxyl 
3. Eudroxyl 
5. Memo to Moore, H. L. from J. S. Scanlan, "Improved Inhaler," is included in OTC Volume 040230.
7. Sanford, T., "Inhaler," Draft of unpublished data is included in OTC Volume 040230.
11. OTC Volume 040230.

1. Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racemic hydrochloride) (oral). The Panel concludes that ephedrine and its salts are safe in the dosage ranges used orally but there are insufficient data to permit final classification of their effectiveness for oral OTC use as nasal decongestants.

(1) Safety. Clinical experience has confirmed that ephedrine and its salts (oral) are safe in the dosage ranges used as a nasal decongestant. Ephedrine has both central and peripheral effects. Ephedrine hydrochloride is a sympathomimetic amines which acts directly on smooth muscles of mucous membranes (decongestion) although this has not been documented. Other peripheral effects include increase of heart rate and tachycardia aggregation of blood pressure, both systolic and diastolic. The cardiovascular and central effects set limits on dosage, limits which vary widely among patients as judged by clinical experience. Anorexia and nausea also occur in some patients. Difficulty in urination may occur in older males with prostatic hypotrophy. Overdosage results in exaggeration of these side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potentially dangerous increases in blood pressure in patients taking monoamine oxidase (MAO) inhibitors.

(2) Effectiveness. There are insufficient studies documenting the effectiveness of ephedrine and its salts (oral) as nasal decongestants. One controlled objective measurement study in patients with nasal obstruction demonstrated nasal decongestant effectiveness of orally administered ephedrine sulfate in doses of 25 mg (Ref. 2). No conclusive data were found to support claims of effectiveness for doses 8 to 12 mg contained in OTC submissions.

(3) Proposed dosage. Adult oral dosage is 8 to 12 mg not more than every 4 hours not to exceed 72 mg in 24 hours. Children 2 to under 6 years oral dosage is 4 to 6 mg not more than every 4 hours not to exceed 30 mg in 24 hours. Children 6 to under 12 years oral dosage is 3 to 3 mg not more than every 4 hours not to exceed 18 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(5) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (see part VIII. paragraph B.1. above—Category I Labeling.)

(6) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestants. (See part VIII. paragraph C. below—Data Required for Evaluation.)

References

4. Memo to Moore, H. L. from J. S. Scanlan, "Improved Inhaler," is included in OTC Volume 040230.
10. OTC Volume 040230.

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(3) Proposed dosage. Adult oral dosage is 8 to 12 mg not more than every 4 hours not to exceed 72 mg in 24 hours. Children 2 to under 6 years oral dosage is 4 to 6 mg not more than every 4 hours not to exceed 30 mg in 24 hours. Children 6 to under 12 years oral dosage is 3 to 3 mg not more than every 4 hours not to exceed 18 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(5) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (see part VIII. paragraph B.1. above—Category I Labeling.)

(6) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestants. (See part VIII. paragraph C. below—Data Required for Evaluation.)

References

4. Memo to Moore, H. L. from J. S. Scanlan, "Improved Inhaler," is included in OTC Volume 040230.
10. OTC Volume 040230.
gestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

In a study of nine patients with head colds, which were self-aggravated by smoking, inhalation of 50 ml volume of eucalyptus vapors did not induce a significant decrease in airway resistance as measured by anterior rhinometry. In addition, it was found that patients taking 300 ml of eucalyptus oil vapors did induce a significant decrease in airway resistance for 15 minutes, but this was followed by increased nasal resistance over the next 100 minutes (Ref. 14).

Other studies involving objective measurement of nasal decongestant activity of eucalyptus oil involved mixtures of volatile substances topically applied as ointments (Refs. 15 through 17). In steam inhalations (Refs. 18 and 19) and room aerosol sprays (Refs. 20 through 22), these studies, although significant nasal decongestant activity as compared to placebo was demonstrated, whether the eucalyptus oil component contributed to this effect is questionable.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms and fewer symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.91 ml/g eucalyptus, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 24).

(3) Proposed dosage. Dosage for adults and children 12 to under 15 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 2 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1-tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, boiled or steamed. Two teaspoonsful of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generally. May be repeated 3 times daily.

(iii) For inhalation use as a 1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at 3/4 to 1 hour intervals as needed.

(iv) For topical use as a lozenge: 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 2 hours.

(v) For use as a mouthwash: 0.91 ml/mg solution: Gargle with 1/2 oz (30 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII, paragraph B.I. above—Category 1 Labeling).

(i) Additional data on the following specific labeling: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

References


(4) Kilman, A. M., "Trunk Rub Study: (Ref. 24), Draft of unpublished data is included in OTC Volume 040288.


(12) Summary of OTC Safety Data is included in OTC Volume 040293.


(23) OTC Volume 040298.

In Menthol/peppermint oil (topical/inhalant). The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(i) Safety. Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Menthol is the chief constituent of peppermint oil, comprising not less than 50 percent, and may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting and symptoms of central nervous system depression such as dizziness, staggering gait, slowed respiration, twitching, and convulsions (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to
stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucosa was subjectively irritating whereas a 0.2 percent solution was judged nonirritating (Ref. 6). A study of 323 subjects in which an ointment containing menthol 2.8 percent was applied for 48 hours to both areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions including contact dermatitis (Ref. 4). A study of 10 subjects who received application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another week of treatment, revealed no local reactions during the challenge phase (Ref. 7). The incidence of hyperirritability to menthol appears to increase with increased duration of use. For example, in one surveillance study involving more than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years whereas an incidence of 3.4 percent hypersensitivity was seen in 144 patients using this type of preparation for longer than 10 years (Ref. 8).

In infants and small children nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and small children requiring treatment who received an ointment containing a mixture of volatile oils including a 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children (23 under 2 years of age) with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children (30 under 2 years of age) received standard therapy plus the mentholated ointment. Nasal airway patency showed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which the recommended doses were not associated with significant complaints of subjective perceived adverse effects (Refs. 11 through 22). Exaggerated use studies in humans and athletes to measure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended volatile substance in the vaporizer, was not associated with irritating or toxic effects (Refs. 24 and 25).

In a study involving 40 healthy subjects who were asked to dissolve 2 candy-base lozenges every 20 minutes for 2 hours, each containing 1.36 mg of menthol together with other volatile oils, exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects (50 adults and 20 children, ages 8 to 12), half of the subjects dissolved a menthol-eucalyptus lozenge, 3.62 mg menthol and 5.35 mg eucalyptus oil, every hour for 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slight discomfort demonstrated on day 1 due to mild irritation of the oral mucosa on days 1 and 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 6.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances containing menthol also has been utilized for treatment of nasal congestion and cough symptoms. Rates exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behavioral response or airway tissues abnormality upon autopsy examination (Ref. 30). A group of 4 monkeys were exposed to an aerosolized mixture of volatile substances for 10 days, the other half dissolved the cough drop base without the aromatics. Inhaled vapors containing 2.8 percent menthol in sufficient degree of nasal decongestion compared to placebo over an 8 hour period as determined by a modified Butler-Ivy procedure (Ref. 30). Two additional objective-measurement placebo-controlled crossover studies involving chest, throat and back application of an ointment containing a mixture of volatile substances including 2.8 percent menthol revealed a significant nasal decongestant effect compared to placebo over an 8 hour period in a total of 80 patients with colds (Refs. 37 and 38).

A liquid mixture of volatile substances which is to be added to the water in a hot steam inhaler containing 6 percent menthol via inhalation contains menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent and vinture of benzoin 0.5 percent. Two objective-measurement placebo-controlled studies in patients with nasal congestion due to head cold revealed that this liquid containing volatile substances placed in hot water in a dose of 1 tablespoon per quart induced a statistically significant decrease in nasal airway resistance compared to inhalation of steam alone during the period of steam inhalation (Refs. 37 and 38). It was demonstrated that an optimal distance between the subject and the vaporizer to elicit this effect was 4 to 6 feet (Ref. 24).

An aerosolized mixture of volatile substances to be sprayed in the room and containing menthol 1 percent and eucalyptus oil 1 percent has been studied for its nasal decongestant effect by ob-
(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.6 percent menthol preparation: To be rubbed on the throat, chest, and back as a thicker layer. The area of application may be covered. However, clothing should be left loose about the head and chest to help the vapors rise to the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation as a 0.42 mg/ml solution: Gargle with ¾ oz (20 ml) twice daily.

(iii) For children under 3 years, there is no recommended dosage except under the advice and supervision of a physician.

(5) Evaluation. The Panel made the following recommendations: (i) For topical preparation: Data to demonstrate effectiveness will be required from one additional controlled objective measurement study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C, below—Data Required for Evaluation.)

(ii) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C, below—Data Required for Evaluation.)

REFERENCES


(7) Larkin, V. P., "Trunk Rub Study (v 331-34)," Draft of unpublished data is included in OTC Volume 040296.


(14) Larkin, V. P., "Vaposteam (Commercial Package), Efficacy and Safety," Draft of unpublished data is included in OTC Volume 040298.


(17) Larkin, V. P., "Clinical Research Studies," Draft of unpublished data is included in OTC Volume 040298.

(18) Amer, A. B., "The Treatment of Respiratory Infections and Toxicity Study of Infants and Children in Polyoxyethylene
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Lauryl Alcohol Vaporization, Draft of unpublished data is included in OTC Volume 040298.

(19) Mund, A., Collection of unpublished data is included in OTC Volume 040298.

(20) Goodell, R., Collection of unpublished data is included in OTC Volume 040298.

(21) Berman, M., Collection of unpublished data is included in OTC Volume 040298.

(22) Singer, A., Collection of unpublished data is included in OTC Volume 040298.

(23) Williams, H., Collection of unpublished data is included in OTC Volume 040298.


(25) Larkin, V. F., "Vaposteam (Commercial Package)," Draft of unpublished data is included in OTC Volume 040298.


(27) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.


(34) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.

(35) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.

(36) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.

(37) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.

(38) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.

(39) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.

(40) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.

(41) Seltzer, S., "Clinical Safety Test on Vicks Cough Drops," Draft of unpublished data is included in OTC Volume 040298.


(47) OTC Volume 040278.

1. Phenylpropanolamine hydrochloride (topical). The Panel concludes that phenylpropanolamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) Safety. Clinical experience has confirmed that phenylpropanolamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Phenylpropanolamine hydrochloride as 1 to 5 percent aqueous solution administered by drops or intranasal tampons was well tolerated by most patients, although a few complained of transient stinging (Refs. 1, 2, and 3). Rhinoscopic examination revealed little or no evidence of nasal irritation following prolonged and continuous use of 3 percent phenylpropanolamine nasal solution but details of time parameters of drug administration were not given (Ref. 2). There is a need for additional data relating frequency of use with incidence and intensity of rebound nasal congestion in adults and children.

(2) Efficacy. There are no well-controlled studies documenting the effectiveness of phenylpropanolamine hydrochloride (topical) as a nasal decongestant. Its effectiveness is uncertain because there are no properly controlled objective measurement studies have been presented.

Phenylpropanolamine hydrochloride is generally considered to exert a nasal decongestant effect typically applied as a 1 to 3 percent solution (Refs. 1 through 5). Administration as drops or soaked intranasal tampons (3 to 5 minutes contact) caused no properly controlled objective measurement studies in their design. No data from studies in children were presented. Studies of nasal decongestant effectiveness of phenylpropanolamine hydrochloride in 0.55 percent to 0.5 percent concentrations are currently in progress and the Panel was told that a report will be submitted when completed (Ref. 6).

(3) Proposed dosage. Adults and children above 6 years of age topical dosage is 2 to 3 sprays of a 1:10 solution in each nostril every 2 hours to 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. Concentrations and frequency of administration should be adjusted to individual usage. Topical use have not been established in children under 6 years.

(4) Labeling. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII, paragraph E.1. above—Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VII, paragraph C. below—Data Required for Evaluation.)

REFERENCES


(6) Letter to Pedotti, W. F. from B. M. Lanman is included in OTC Volume 040298.

J. Thenyldiamine hydrochloride (topical). The Panel concludes that thenyldiamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of thenyldiamine hydrochloride as safe and effective for OTC use as a nasal decongestant.

(1) Safety. Clinical experience has confirmed that thenyldiamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant.

(2) Efficacy. There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (topical) as a nasal decongestant.

(3) Proposed dosage. Adults and children above 6 years of age topical dosage is 0.1 percent or 0.2 percent thenyldiamine hydrochloride in combination with phenylephrine hydrochloride, 0.25 and 0.5 percent, produced only "slight" or "moderate" stinging in some of the subjects in human intranasal irritation studies conducted by a manufacturer (Ref. 1). Preparations containing 0.5 percent thenyldiamine hydrochloride produced moderate to "severe" stinging in all subjects and irritation of the larynx in a few subjects. There are no data available on the incidence of rebound congestion.

(4) Labeling. There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (topical) as a nasal decongestant. In a randomized, double-blind, and
crossover study of patients with acute rhinitis, a combination of thymylamine hydrochloride, 0.1 percent, with other active ingredients applied intranasally as a sprayed solution produced a subjectively evaluated nasal decongestant effect which was significant as compared to that produced by a placebo solution (Ref. 2). However, in this study the effectiveness of the combination product, thymylamine with phenylephrine and benzalkonium, was not significantly different from that of the product minus thymylamine. In fact, the nasal decongestant effect produced by phenylephrine alone and the nasal decongestant effect produced by thymylamine alone were not significantly different from each other. The nasal decongestant effect produced by the combination commercial product. The three preparations did not differ at the 95 percent confidence level.

In another controlled study to determine the therapeutic contribution of topically applied thymylamine in a combination product with phenylephrine and benzalkonium, no additive or synergistic decongestant effect was obtained by phenylephrine 0.5 percent alone, when measured by posterior electronic rhinometry or by a plethysmographic nose model (Ref. 3).

The manufacturer's labeling states that thymylamine hydrochloride "offsets the results of mediator release to the extent it is producing obstruction and at the same time opposes cholinergic hypersecretion'" (Ref. 4). Thymylamine is presumed to be a plethysmographic nose model (Ref. 3).

The manufacturer's labeling states that thymylamine hydrochloride "offsets the results of mediator release to the extent it is producing obstruction and at the same time opposes cholinergic hypersecretion and rhinorrhea." Thacker (Ref. 4) supports inclusion of antihistamines in OTC nasal decongestant products to prevent engorgement from migration of excessive blood into the veins that feed into tissue spaces and to aid in alleviating allergic reactions to ingredients in the solution. This supposition, however, is not supported by scientific evidence.

Studies with topical thymylamine indicate it may be a nasal decongestant but no nasal decongestant claims are made for this ingredient in the commercially available products. Although the products themselves are nasal decongestants, present claims made for thymylamine are based on topical application of an antihistamine but there are no studies on the antihistamine activity of the drug applied topically.

There are no data on the use of this drug in children.

(3) Proposed dosage. Adult topical dosage is 1 to 3 drops or sprays of a 0.1 percent solution in each nostril not more than every 4 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category B labeling for nasal decongestant active ingredients. (See part VIII, paragraph C.1. above—Category B Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

REFERENCES


(3) Gould, W. J., "Clinical Summary of OTC compounds." Draft of unpublished paper is included in OTC Volume 40, section 167.


(5) Safety. Clinical experience has apparently confirmed that thymylamine inhalant is safe in the dosage ranges used as a nasal decongestant.

Thymylamine is an alkyl derivative of phenol and has bactericidal, fungicidal, and antifungal properties (Ref. 1). When hydrolyzed, thymylamine is converted to the cleavage aldehyde, thimyldehyde (Ref. 2).

The LDA of thymylamine in mice is 1,800 mg/ kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymylamine's relatively inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymylamine is presumed to be relatively nontoxic.

(6) Effectiveness. There are no well-controlled studies documenting the effectiveness of thymylamine (inhalant) as a nasal decongestant. Experiments in anesthetized rabbits have indicated that thymylamine administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2).

The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymylamine alone were found although a mixture containing thymylamine, menthol, eucalyptus, and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the nasal decongestant activity of thymylamine were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8, and 9), and in steam inhalations (Refs. 10 and 11). Although nasal decongestant activity as compared to placebo was demonstrated, it was not evident whether the thymylamine component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.63 mg/ml thymylamine, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (1) For topical use as a 0.1 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to the nose and mouth. Applications may be repeated up to 3 times daily.

(2) For steam inhalation use as a 0.1 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of hot water. Inhale the vapors during the period of medicated steam generation. May be repeated 3 times daily.

(3) For inhalation use as a 0.1 percent solution: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(4) For topical use as a lozenge 0.02 to 0.2 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(5) For use as a mouthwash 0.63 mg/ml solution: Gargle with ½ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category B labeling for nasal decongestant active ingredients. (See part VIII, paragraph C.1. above—Category B Labeling.) In addition, the Panel recommends the following specific labeling:

(1) For topical ointment use: Warning: "For external use only. Do not take by mouth." (2) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth.

(6) Evaluation. The Panel made the following recommendations: (3) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(2) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(3) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)
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(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

REFERENCES


(3) Inhaled Menthol and Thymol," CRD 71-1, (Draft of unpublished data is included in OTC Volume 040298.)

(4) Labeling.) In addition, the Panel recommends the following specific labeling: (I) For topical use as a lozenge- Data Required for Evaluation.

(5) The Panel made the following recommendations: (I) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

REFERENCES


(2) Borland, G. F. and Blanche, V.-L., "Vapors-Levels of Aromatic From a Vaporizer," is included in OTC Volume 040286.

(3) Memo to Hoffman, G. F. from A. F. Blanchette, "Vaporub—Levels of Aromatic From a Vaporizer," is included in OTC Volume 040286.


(13) Larkin, V. D., "VAPOURUB in Hot Water," Draft of unpublished data is included in OTC Volume 040298.

(14) OTC Volume 040278.

1. Turpentine oil (spirits of turpen- time) (topical/inhalant). The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) The Panel recommends the Category I labeling for nasal decongestants—(See part VIII, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (I) For topical use: Warning: "For external use only. Do not take by mouth or place in nostrils." (ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth." (5) Evaluation. The Panel made the following recommendations: (I) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(iii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)
classification of the labeling claims identified below for nasal decongestants. Additional data are required to support the following nasal decongestant claims:

Reference to "preventing sneezing," "drying runny nose" or "clearing" nasal drip" are unsubstantiated claims for nasal decongestants unless studies specifically designed to assess these activities are presented. Studies of nasal decongestants have assessed the effect on nasal airway resistance or the ease of breathing but not the effect on rhinorrhea.

Reference to an indirect effect in "preventing or alleviating cough" by an effect on nasal congestion is an unsubstantiated claim unless studies specifically designed to assess this activity are presented.

Reference to an effect "to reduce sinus pressure" is an unsubstantiated claim since studies of nasal decongestant activity assess the effect on nasal airway resistance. Although it is assumed that this effect on the nasal mucosa may indirectly facilitate sinus drainage and thus decrease sinus congestion, it would be unsubstantiated if it is claimed as an effect to decrease sinus pressure without evidence to support this claim.

Reference to the extent of the penetration of topical nasal decongestants is unsubstantiated without specific studies to demonstrate the extent of penetration (depth of penetration into the nasal cavity and/or the extent of penetration into nasal mucosal pressure)

Pressure within the antrum can be measured and recorded in terms of centimeter of water compared to ambient pressure by means of a suitable needle or small trocar placed in the antrum under topical anesthesia. This would be performed in a small number of patients (5 to 10) with nasal congestion associated with an acute respiratory infection who complain of localized headache and/or tenderness in the sinus areas. These pressure measurements would be repeated following the administration of the test preparation or placebo in the dosage range and time intervals recommended for OTC usage. Subjective symptoms such as headache, tenderness, etc., could be recorded in connection with the pressure measurements.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. Principles in the design of an experimental protocol for testing nasal decongestant drugs. a. General principles. The effectiveness of a nasal decongestant drug should be determined by its ability to reduce nasal obstruction in patients with acute rhinitis. The drug should involve double-blind placebo-controlled assessment of the drug's ability to decrease nasal airway resistance. Patient-reported subjective assessment is also desirable. The drug used should be the same as in the OTC preparation and should be given in the same dosage as the recommended labeling instructions for the preparation. Since either oral or topical nasal decongestants may be administered repeatedly during episodes of nasal congestion, studies should bear on the appropriate use of the drug to maintain optimal relief of symptoms. For locally applied nasal decongestants, wherein rebound congestion with repeated use is a concern, labeling should specify short-term use in providing temporary relief of nasal congestion. Specific data on this matter should be obtained by testing the topical nasal decongestant in the concentrations and maximal dosage frequencies to be recommended for periods of at least 1 week in order to assess the incidence and severity of a drug-induced increase in nasal airway resistance.

b. Selection of patients. Selection of patients for testing should be based on the diagnosis of rhinitis with nasal congestion. Patients with chronic allergic or vasomotor rhinitis present relatively stable nasal congestion and consequently would not serve as the most valid test to a crossover study design. Patients with acute allergic or infectious rhinitis also represent a large proportion of the patient type likely to self-medicate with a nasal decongestant. Thus, the relatively brief time course of these acute disorders and greater variation in stability of congestion, larger numbers of these patients would be studied by assigning them in random fashion to placebo or drug groups. Further, for comparative purposes these groups have to be matched by age, sex, and if possible, the extent of nasal congestion at the time of the study. Smoking by test subjects should be prohibited 24 hours prior to and during the test.

c. Methods of study. Observation should include both the subjective response and objectively measured nasal airway resistance before the drug or placebo is administered, and at appropriate intervals thereafter to demonstrate time of onset, magnitude, and duration of response.

d. Interpretation of data. A recommended dose of the test drug should induce a statistically significant reduction in nasal airway resistance when compared with the placebo response.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories. All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. Evaluation of safety. Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to a maximum therapeutic effectiveness.

IX. MISCELLANEOUS INGREDIENTS

A. GENERAL COMMENT

The action of several drugs considered by the Panel to be within the main pharmacologic groups, i.e., antihistamines, decongestants, bronchodilators, anticoagulants, and local anesthetics for nasal decongestants reviewed by the Panel. However, these miscellaneous ingredients are found in many OTC CCABA products. Because of the differences in their in-use labeling for OTC products, they are discussed individually below.

d. CATEGORIZATION OF DATA

The miscellaneous ingredients and/or labeling have been reviewed and classified as follows:

1. Conditions under which CCABA products are not generally recognized as safe and effective. Certain drugs are currently available for use at bedtime and promoted for such various claims as "for restful sleep". However, the duration of drug effects in "night-time cold preparations" phrased in this manner are currently available for use at bedtime and promoted for such various claims as "restful sleep". However, the duration of drug effects in "night-time cold preparations" phrased in this manner (see part II, paragraph C.5.b., above—Combination products containing antihistamines with sleep-aid claims).

Certain antihistamines are generally considered safe for OTC use. The Panel has recommended specific doses for each of these antihistamines after a consideration of the scientific data available for these ingredients. The Panel concluded that the antihistamines reviewed by the Panel and classified as Category I are both safe and effective for the treatment of symptoms of allergic rhinitis. (See part VII, paragraph B.1., above—Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.) However, the Panel does not recommend the addition of another antihistamine to a CCABA combination product for the purpose of sedation. The rationale for the removal of additional antihistamine in CCABA combination products for the exclusive purpose of sedation has not been demonstrated.

2. Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold". The Panel is aware of one well-controlled study documenting the safety and effectiveness of such use.
of vitamins for use in the prevention or treatment of the "common cold." In addition, the Panel concludes that the use of any vitamin in CCABA combination products for the prevention of colds is irrational since such products should only be used to treat symptoms of the "common cold." The Panel has discussed this issue earlier in this document. (See part II, paragraph C.5.a. above—Combination products containing vitamins.)

The Panel is aware of the popular use of vitamin C for treatment of the symptoms of the "common cold." However, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." Meanwhile, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." Nevertheless, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." Therefore, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." In addition, the Panel concludes that the use of any vitamin in CCABA combination products for the prevention of colds is irrational since such products should only be used to treat symptoms of the "common cold." The Panel has discussed this issue earlier in this document. (See part II, paragraph C.5.a. above—Combination products containing vitamins.)

The Panel is aware of the popular use of vitamin C for treatment of the symptoms of the "common cold." However, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." Therefore, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." In addition, the Panel concludes that the use of any vitamin in CCABA combination products for the prevention of colds is irrational since such products should only be used to treat symptoms of the "common cold." The Panel has discussed this issue earlier in this document. (See part II, paragraph C.5.a. above—Combination products containing vitamins.)

The Panel is aware of the popular use of vitamin C for treatment of the symptoms of the "common cold." However, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." Therefore, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold." In addition, the Panel concludes that the use of any vitamin in CCABA combination products for the prevention of colds is irrational since such products should only be used to treat symptoms of the "common cold." The Panel has discussed this issue earlier in this document. (See part II, paragraph C.5.a. above—Combination products containing vitamins.)
milder illness than those receiving a placebo. (Ref. 12) These findings indicate that very large daily doses of vitamin C may be unnecessary.

In a recent study (Ref. 13), a random sample of employees in the National Institutes of Health comprising 190 subjects were given prophylactic daily ascorbic acid dosage of 100 mg per day for 8 weeks and with the onset of a "cold" were given 3,000 mg or 6,000 mg ascorbic acid or a placebo. The study was well-designed with the exception that the placebo differed in taste from the active drug thus leading the investigators to question whether the observed result of "minor influence on the duration and severity of colds" was attributable to this flaw in the study design rather than to a beneficial effect of ascorbic acid.

One means by which vitamin C might favorably influence the "common cold" is suggested by recent in vitro studies showing that in the presence of 250 mcg/ ml vitamin C and glutathione, the growth of one of the causes of the "common cold" was inhibited. (Ref. 14) In contrast to the paper cited for the antiviral effect, one of the recent clinical studies indicates that vitamin C has a beneficial effect on various types of illnesses and not only Q fever syndrome referred to as the "common cold" (Ref. 11).

The Panel concludes that the published data support a beneficial effect of vitamin C on the severity and perhaps frequency of the "common cold" when given in dosages exceeding the daily requirement. However, it is not yet clear that this effect is clinically significant.

The magnitude of the dosages needed and the optimum schedule for prophylaxis and therapy remain to be determined.

3. Proposed dosage. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable "proposed dosage for testing."

4. Labeling. The Panel is unable to determine drug labeling claims. The Panel concludes that no drug labeling claims should be made for vitamin C. The Panel recognizes that vitamin C is readily available as a food supplement and that products with labeling claims for the prevention or treatment of the "common cold" are subject to abuse. The Panel recommends that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as licensed on the manufacturer's marketed product(s).

5. Evaluation. Data to demonstrate effectiveness as a stimulant corrective will be required to be completed in 2 years. An acceptable test procedure will be the one described for combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence or intensity of the undesirable side effect and the safety of this combination.

d. Phenobarbital. The Panel concludes that there are insufficient data to permit final classification of phenobarbital as safe and effective for OTC use as a "stimulant corrective" in combination products with central nervous system stimulant drugs, such as the theophyllines and ephedrine. The Panel concludes that phenobarbital has been added as a "sedative corrective" rather than as a CCABA active ingredient. The Panel has discussed this issue earlier in this document. (See part II, paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) Safety. Clinical experience has confirmed that phenobarbital is generally considered safe in the doses recommended for sedative effect. The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg commonly contained in CCABA combination products.

The Panel is aware of the OTC Sedative, Tranquilizer and Sleep-Aid Drug Product Panel's discussion regarding caffeine which were published in the Federal Register of December 8, 1975 (40 FR 17299). That Panel concluded that caffeine when used alone and not in combination with a sedative drug product is safe and effective for use as a stimulant at a recommended dose of 100 to 200 mg not more often than every 3 to 4 hours. A review of the well-controlled studies demonstrating the effectiveness of caffeine as a "stimulant corrective" in combination CCABA products.

The Panel is unaware of any data that support such use in combination products.

3. Proposed dosage. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as licensed on the manufacturer's marketed product(s).

4. Labeling. The Panel recommends the labeling claims contained in each manufacturer's currently marketed products. In addition, the Panel recommends the activity of caffeine should be identified on the label as "an ingredient added to counteract drowsiness caused by other drugs in this product."

5. Evaluation. Data to demonstrate effectiveness as a stimulant corrective will be required to be completed in 2 years. An acceptable test procedure will be the one described for combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence or intensity of the undesirable side effect and the safety of this combination.

References


Caffeine. The Panel concludes that there are insufficient data to permit final classification of caffeine as safe and effective for use as a "stimulant corrective" in combination products containing central nervous system sedating drugs, such as the antihistamines. The Panel presumes that caffeine has been added as a "stimulant corrective" rather than as a CCABA active ingredient. The Panel has discussed this issue earlier in this document. (See part II, paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) Safety. Clinical experience has confirmed that caffeine is generally considered safe in the doses recommended for sedative effect. The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg commonly contained in CCABA combination products.

The Panel is aware of the OTC Sedative, Tranquilizer and Sleep-Aid Drug Product Panel’s discussion regarding caffeine which were published in the Federal Register of December 8, 1975 (40 FR 17299). That Panel concluded that caffeine when used alone and not in combination with a sedative drug product is safe and effective for use as a stimulant at a recommended dose of 100 to 200 mg not more often than every 3 to 4 hours. A review of the well-controlled studies demonstrating the effectiveness of caffeine as a "stimulant corrective" in combination CCABA products.

The Panel is unaware of any data that support such use in combination products.

3. Proposed dosage. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as licensed on the manufacturer’s marketed product(s).

4. Labeling. The Panel recommends the labeling claims contained in each manufacturer’s currently marketed products. In addition, the Panel recommends the activity of caffeine should be identified on the label as “an ingredient added to counteract drowsiness caused by other drugs in this product.”

5. Evaluation. Data to demonstrate effectiveness as a stimulant corrective will be required to be completed in 2 years. An acceptable test procedure will be the one described for combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence or intensity of the undesirable side effect and the safety of this combination.

d. Phenobarbital. The Panel concludes that there are insufficient data to permit final classification of phenobarbital as safe and effective for OTC use as a “stimulant corrective” in combination products with central nervous system stimulant drugs, such as the theophyllines and ephedrine. The Panel presumes that phenobarbital has been added as a “sedative corrective” rather than as a CCABA active ingredient. The Panel has discussed this issue earlier in this document. (See part II, paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)
theophyllines and epinephrine, at a dose of 8 mg, to counteract the central nervous stimulant effect of these drugs. However, the effectiveness of phenobarbital as a "sedative corrective" at a dose of 8 mg has not been established.

The generally accepted dosage of phenobarbital as a sedative is 15 to 30 mg given 2 to 4 times daily (Refs. 1 through 5). It would be reasonable to expect that some stimulation from other drugs such as ephedrine, the dose to antagonize the stimulation should be at least the minimum effective sedation dose. All the citations in the various volumes submitted state only that a barbiturate is useful in countering the stimulant effects of drugs like ephedrine. None suggest a dose. Phenobarbital stimulates hepatic enzymes which may increase the metabolism of other drugs and thereby reduce their expected activity (Refs. 1 and 2). It would seem that the only way to determine the effectiveness of an 8 mg dose of phenobarbital and whether it contributes to the combination of antiasthmatic preparations is by conducting controlled clinical trials.

Adult therapeutic dosage is 8 to 16 mg every 4 hours.

(4) Labeling. The Panel recommends the following: (i) Indications. The activity or theophylline should be identified on the label as an "ingredient added to counteract nervousness caused by other drugs in this product".

(ii) Warnings. (a) "Caution: May cause drowsiness. Avoid driving a motor vehicle or operating heavy machinery".

(b) "Do not take this product if you are presently taking other drugs except under the advice and supervision of a doctor".

(c) "May be habit-forming".

(5) Evaluation. Effectiveness at 8 mg has not been established. Further studies must be completed in 2 years. The Panel recommends the following guidelines to establish effectiveness as a "sedative corrective":

a. General Principles. Symptomatically drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this a small dose of sedative has been added to some combinations. All preparations should be designed to evaluate the effectiveness of the sedative under the above circumstances and, in addition, it is necessary to show whether the sedative has any additional beneficial or adverse effects on bronchospasm.

b. Selection of Patients. Testing should be based on results of a double-blind crossover study. There should be generalized airway obstruction whose severity varies greatly over a short period of time and should be demonstrated by pulmonary function tests with significant improvement occurring after the use of a Category I bronchodilator drug.

c. Methods of Study. The study should consist of a double-blind crossover design. The preparations should be given 1/2 hour before meals to be sure of good absorption. It is suggested that the preparation be given at the manufacturer's suggested dosage 4 times daily for 5 days, and then a crossover alternate be given for a similar period.

Two methods of evaluating the preparation should be involved:

(i) There should be a questionnaire with questions related to nervousness, insomnia, irritability, and tremor. There should also be questions related to the patient's assessment of change in his asthmatic condition. The questionnaire might best be developed in the form of a diary.

(ii) Pulmonary function tests and blood gas estimations: The latter are important to determine if the sedative is producing any respiratory depressant effect. These determinations should be done at the beginning of the trial and at the end of the trial before taking the first dose and 1 hour after taking the first dose. Therefore, there should be sets of pulmonary function tests as follows:

(a) First preparation (bronchodilator alone or with a sedative): One half hour before taking the first dose of the first preparation and 1 hour after taking the first dose of the first preparation.

(b) As above at the end of the 5 days when the last dose of the first preparation is taken.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both evidence of drug effectiveness and evidence of acceptable safety. The results of animal or clinical studies based on the results of two different investigators or laboratories are necessary to establish the drug to be "generally recognized as safe and effective".


PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR AND ANTIASTHMATIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

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Subpart B—Active Ingredients

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Subpart A—General Provisions

§ 341.1 Scope.

An over-the-counter cold, cough, allergy, bronchodilator or antiasthmatic product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.
§ 341.3 Definitions.

As used in this part:

(a) Age (dosage) range. Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

(b) Allergy product. A drug product used for the relief of the symptoms of allergic rhinitis, such as hay fever.

(c) Anticholinergic drug. A drug used for the relief of the symptoms of mild allergic rhinitis, such as hay fever (seasonal allergic rhinitis) and perennial allergic rhinitis.

(d) Antihistaminic drug. A drug which inhibits or controls the act of coughing.

(e) Asthma product. A drug product used for the control of the symptoms of bronchial asthma.

(f) Bronchodilator drug. A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the asthmatic treatment of wheezing and shortness of breath.

(g) Cough product. A drug product used to inhibit, control or suppress the act of coughing.

(h) Expectorant drug. A drug used to promote or facilitate the removal of secretions from the respiratory airways.

(i) Hay fever product. A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(j) Inhalant dosage. The dosage range that is generally recognized as safe and effective by mouth or by nasal external rub or as an inhalation.

(k) Nasal decongestant drug. A drug which reduces nasal congestion caused by acute or chronic rhinitis.

(l) Oral dosage. The dosage range that is generally recognized as safe and effective by mouth.

(m) Topical dosage. The dosage range that is generally recognized as safe and effective by topical rub, such as the external rub for inhalation, as a local application by mouth, or as drops or sprays for local application intranasally.

Subpart B—Active Ingredients

§ 341.12 Antihistaminics.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) Brompheniramine maleate. Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(b). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) Chlorpheniramine maleate. Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(a). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) Diphenhydramine hydrochloride. Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) Doxylamine succinate. Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(f). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) Methapyrilene hydrochloride. Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 125 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(d). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) Phenylpropanolamine. Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(g). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(g) Pheniramine maleate. Adult oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(h). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(h) Promethazine hydrochloride. Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 25 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(i). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(i) Pyrilamine maleate. Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(j). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(j) Thonzylamine hydrochloride. Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 200 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(l). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.14 Antitussives.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate). (1) Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) Shall apply to products pursuant to the requirements identified in § 384.20(a) and § 1308.15(b) of this chapter.

(b) Dextromethorphan, dextromethorphan hydrobromide. Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) Diphenhydramine hydrochloride. Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.16 Bronchodilators.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) Ephedrine preparations. (ephedrine, ephedra hydrochloride, ephedrine sulfate, racephedrine hydrochloride). Adult oral dosage is 12.5 to 25 mg less often than every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is identified in § 341.90(e). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) Epinephrine preparations. (epinephrine, epinephrine bitartrate, epi-
neophylline hydrochloride (racemic) (inhalant). Adults and children 4 years and above Inhalation dosage is 1 to 3 inhalations of a 1 percent aqueous solution of 1-epinephrine or the equivalent in a pressurized preparation not more often than every 3 hours, except under the advice and supervision of a physician. Children under 4 years, there is no recommended dosage except under the advice and supervision of a physician. 

Children and adolescents should not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if excessively used. 

There is the possibility of abuse of this inhaler. Only drops should be used in children 2 to under 6 years of age except under the advice and supervision of a physician. 

If excessively used, theophylline preparations (aminoephedrine, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate). Adult oral dosage is 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician. 

(d) Theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate). Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 200 mg every 4 to 6 hours not to exceed 800 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in § 341.90(k). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician. 

(c) Methoxypenamine hydrochloride. Adult oral dosage is 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician. 

(b) Naphazoline hydrochloride (topical). Adult topical dosage is 1 to 2 drops or sprays in each nostril not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 or 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. Children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. 

(a) Ephedrine preparations (ephedrine, ephedrinophosphate, ephedrine sulfate, racephedrine hydrochloride) (topical). Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 or 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. Children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. 

Any single antihistamine active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective antihistamine-antipyrine active ingredient: Provided, That the combination contains any applicable labeling identified in § 341.85(d). 

(d) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20. 

Any single antitussive active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single generally recognized as safe and effective nasal-antipyrine active ingredient: Provided, That the combination contains the labeling identified in § 341.85(d). 

Any single antihistamine active ingredient identified in § 341.14 may be combined with any single bronchodilator active ingredient identified in § 341.16: Provided, That the combination contains the labeling identified in § 341.85(b). 

Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20. 

Any single antitussive active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective expectorant active ingredient. 

Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single generally recognized as safe and effective local anesthetic or local analgesic active ingredient.
granted: Provided, That the product is available only as a lozenge.

(k) Any single bronchodilator active ingredient identified in § 341.16(a) may be combined with any single generally recognized as safe and effective expectorant active ingredient: Provided, That the combination contains the labeling identified in § 341.85(e).

(3) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: Provided, That the combination contains the labeling identified in § 341.85(d).

(m) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective local anesthetic or local anesthetic active ingredient: Provided, That the product is available only as a lozenge.

Subpart C—Testing Procedures

§ 341.45 Theophylline tablet dissolution testing.

All tablet product formulations containing theophylline, preparation(s) identified in § 341.16(d) shall be tested according to the procedures described in the United States Pharmacopeia XIX (page 651). The tablets shall be suitable for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount, based on the anhydrous theophylline, equivalent content, and the quantity of theophylline dissolved within 30 minutes is not less than 90 percent of the labeled amount of theophylline, based on the anhydrous theophylline equivalent content, for each of the tablets tested. The resulting data shall be submitted by petition to the Food and Drug Administration for approval prior to use. The petition and the data contained therein shall be maintained in a permanent file for public review by the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

Subpart D—Labeling

§ 341.50 Labeling of cold, cough, allergy, bronchodilator, and antiasthmatic products.

(a) Indications. (1) The labeling shall identify the product pursuant to the appropriate definition(s) established in § 341.3 and shall contain the applicable labeling for the active ingredient(s) as set forth in §§ 341.70, 341.72, 341.74, 341.76, 341.78, and 341.80.

(2) In addition, labeling may also contain the following indication(s): Provided, That such phrase(s) is combined and contiguous with the indications required as set forth in § 341.50(a)(1):

(i) "as may be associated with the common cold (cold)."

(ii) "as may occur in the common cold (cold)."

(b) Directions for use. The labeling of the product shall contain the recommended dosage, dosage schedule, and duration of treatment, where appropriate, established in §§ 341.12, 341.14, 341.16, or 341.20 under the heading "Directions," per time interval, e.g., every 4 hours, or other time period, e.g., 3 times daily, broken down by age groups, if appropriate, followed by "or as directed by a physician."

(c) Warnings. The labeling of the product shall contain the appropriate warning(s) under §§ 341.70, 341.72, 341.74, 341.76, 341.78, or 341.80 and, if applicable, the following general warning under the heading "Warning," which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable. For products containing an alcoholic content greater than 10 percent (weight/weight) "Do not give this product to children under 6 years except under the advice and supervision of a physician."

(d) Drug interaction precautions. The labeling of the product shall include under the heading "Drug Interaction Precautions", § 341.70 Products containing anticoagulants.

(a) Indications. The labeling of the product shall contain any of the following Indications under the heading "Indications":

(1) For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract.

(2) Temporarily suppresses watery discharge.

(3) Temporarily relieves excessive nasal secretions.

(4) Temporarily relieves itching of the nose or throat.

(5) Temporarily suppresses watery eyes.

(b) Warnings. The labeling of the product shall contain the following warnings, under the heading "Warnings":

(1) Do not exceed recommended dosage except under the advice and supervision of a physician.

(2) Do not continue to take this product if constipation, excessive dryness of the mouth; insomnia, excitement, confusion, rapid pulse, or blurring of vision occur.

(3) "Caution: Do not take this product if you have asthma, bronchitis or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician."

(4) "Do not give this product to children under 6 years except under the advice and supervision of a physician."

§ 341.72 Products containing antihistamines.

(a) Indications. The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "Alleviates, decreases, or for temporary relief of, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)."

(2) "Alleviates, decreases, or for temporary relief of, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)."

(3) "Alleviates, decreases, or for temporary relief of, running nose, sneezing and itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)."

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)."

(5) "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)."

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)."

(b) Warnings. The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "Caution: Avoid driving a motor vehicle or operating heavy machinery."

(2) "Caution: Avoid alcoholic beverages while taking this product."

(3) "Do not give this product to children under 6 years except under the advice and supervision of a physician."

(4) "For products containing the active ingredients identified in paragraphs (a), (b), (d), (g), and (h) of § 341.12: May cause marked drowsiness."

(5) "For products containing active ingredients identified in paragraphs (c), (d), (e), (g), and (h) of § 341.12: Caution: May cause nervousness and insomnia in some individuals."

§ 341.74 Products containing antihistamines.

(a) Indications. The labeling of the product may contain any of the following indications, under the heading "Indications": (1) "Cough suppressant which temporarily reduces the impulse to cough."

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or due to inhaled irritants."

(3) "Temporarily quiet coughing by its antitussive action."

(4) "Temporarily helps you cough less."

(5) "Temporarily helps quiet the cough reflex that causes coughing."

(6) "For products containing an ingredient identified in § 341.14(a): "Calm the cough control center and relieves coughing."

(7) "For products containing an ingredient identified in § 341.14(b) and (c):..."
(1) "Causes the cough control center and relieves coughing."
(2) "Non-narcotic cough suppressant for the temporary control of coughs."
(3) "Causes cough impulses without narcotics."

(b) **Warnings.** The labeling of the product contains the following warnings, under the heading "Warnings":
(1) "Do not give this product to children under 2 years except under the advice and supervision of a physician."
(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician."
(3) "Caution: A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician."
(4) For products containing an ingredient identified in § 341.14(a):
   (i) "May cause or aggravate constipation."
   (ii) "Do not give this product to children taking other drugs except under the advice and supervision of a physician."
   (iii) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician."
(5) For products containing an ingredient identified in § 341.14(g):
   (i) "May cause marked drowsiness."
   (ii) "May cause excitability especially in children."
   (iii) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician."
   (iv) "Caution: Avoid driving a motor vehicle or operating heavy machinery."
   (v) "Do not give this product to children under 6 years except under the advice and supervision of a physician."

§ 341.76 Products containing bronchodilators
(a) **Indications.** (1) The labeling of a product to be taken by inhalation may contain under the heading "Indications" the time to onset of action expressed in minutes.
(2) The labeling of the product shall contain any of the following indications, under the heading "Indications":
   (i) "For temporary relief of bronchial asthma."
   (ii) "For symptomatic control of bronchial asthma."
   (iii) "Provides temporary relief from acute symptoms of bronchial asthma."
   (iv) "Relaxes tense bronchial muscles to ease breathing for asthma patients."
   (v) "For temporary relief of wheezing (attacks and distress) of bronchial asthma."

(b) **Warnings.** The labeling of the product contains the following warning, under the heading "Warnings":
(1) "Caution: Do not take this product unless a diagnosis of asthma has been made by a physician."
(1) For products containing topical nasal decongestants:  
   (i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge, or more than one person may spread infection."
   (ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician."
   (iii) "The use of this dispenser by more than one person may spread infection."
(2) For products used as oral nasal decongestants:  
   (i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur."
   (ii) "If symptoms do not improve within 7 days or are accompanied by high fever, consult a physician before continuing use."
   (iii) "Do not take this preparation if you have high blood pressure, heart disease, diabetes, or thyroid disease except under the advice and supervision of a physician."  
(3) For products used as inhalant nasal decongestants: 
   (i) "This inhaler should be warmed in hand before use to increase effectiveness."
   (ii) "Do not give this product to children under 2 years except under the advice and supervision of a physician."
   (iii) "Do not exceed recommended dosage at a concentration of 0.125 percent."
(4) For products containing the active ingredient identified in § 341.20(a) at a concentration of 0.5 percent:  
   (a) "This inhaler should be warmed in hand before use to increase effectiveness."
   (b) "Caution: Not for use by mouth."
(5) For products containing the active ingredient identified in § 341.40(d) shall contain the following warning under the heading "Warning:" 
   "Drug interaction precaution: Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician."
§ 341.25 Labeling of combinations of active ingredients.
(a) Antihistamine combined with an antitussive. A combination identified in § 341.40(g) shall contain the following warning under the heading "Warning:"  
(b) Bronchodilator combined with an expectorant. A combination identified in § 341.40(f) shall contain the following warning under the heading "Warning:"  
(c) Aspirin (acetylsalicylic acid) containing combinations. Any combination identified in § 341.40(a), (b), or (m) containing aspirin (acetylsalicylic acid) shall contain the following warning, under the heading "Warning:"  
§ 341.90 Professional labeling.  
The labeling of the product provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredient identified below:  
(a) For products containing brompheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.  
(b) For products containing chlorpheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.  
(c) For products containing diphenhydramine hydrochloride:  
   (1) "Do use as an antihistamine: Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours."
   (2) "Do use as an antitussive: Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours."
   (d) For products containing doxylamine succinate: Children 2 to under 6 years oral dosage is 1.5 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.  
(e) For products containing ephedrine preparations for use as a bronchodilator (ephedrine, ephedrine hydrochloride, ephedrine sulfate, ephedrine hydrochloride and pseudoephedrine sulfate): Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg not more often than every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 0.3 to 0.5 mg/kg of body weight not more often than every 4 hours not to exceed 2 mg/kg of body weight in 24 hours.  
(f) For products containing methapyrine preparations (methapyrine fumarate, methapyrine hydrochloride): Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.  
(g) For products containing phenindamine tartrate: Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.  
(h) For products containing pheniramine maleate: Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.  
(i) For products containing promethazine hydrochloride: Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.  
(j) For products containing pyrilamine maleate: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.  
(k) For products containing theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate): Children 2 to under 12 years oral dosage based on the anhydrous theophylline equivalent is 3.33 mg/kg of body weight 3 times daily every 6 hours not to exceed 10 mg/kg in 24 hours.  
(l) For products containing thonzylamine hydrochloride: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.
Interested persons are invited to submit their comments in writing (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before December 8, 1976. Such comments should be addressed to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before January 7, 1977. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 30, 1976.

SHERWIN GARDNER,  
Acting Commissioner of Food and Drugs.
THURSDAY, SEPTEMBER 9, 1976

PART III:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

RECOMBINANT DNA RESEARCH GUIDELINES

Draft Environmental Impact Statement
NOTICES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
National Institutes of Health

RECOMBINANT DNA RESEARCH GUIDELINES

Draft Environmental Impact Statement

On Wednesday, June 23, 1976, the Director of the National Institutes of Health, with the concurrence of the Secretary of Health, Education, and Welfare, and the Assistant Secretary for Health, issued Guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules.

The decision by the NIH Director to release the Guidelines was reached after extensive scientific and public airing of the issues. The issues were discussed at public meetings of the Recombinant DNA Molecule Program Advisory Committee (Recombinant Advisory Committee) and the Advisory Committee to the NIH Director. The Recombinant Advisory Committee debated three different versions of the Guidelines during this period, and made detailed recommendations to the NIH Director on how this line of research could be effectively controlled with maximum protection of workers and the environment against possible hazards.

The Advisory Committee to the NIH Director, augmented with consultants representing law, ethics, consumer affairs, and the environment, was asked to advise on whether the proposed Guidelines balanced responsibility to protect the public with the potential benefits through the pursuit of new knowledge. The many points of view expressed at an open meeting of the Committee on February 9 and 10, 1976, and in subsequent correspondence, were taken into consideration in the Director's decision.

A number of public commentators urged NIH to consider preparing an environmental impact statement on recombinant DNA research activity. They evoked the possibility that organisms containing recombinant DNA molecules might escape from the environment in potentially harmful ways. It should be noted that the development of the guidelines was in large part tantamount to conducting an environmental impact assessment. For example, the objectives of recombinant DNA research were considered and the potential hazards and risks analyzed. Possible alternative approaches to the objectives were thoroughly explored, to maximize safety and minimize potential risks. And an elaborate review structure to ensure safety has been constructed.

The Guidelines are premised on physical and biological containment to prevent the release or propagation of DNA recombinants outside the laboratory. Deliberate release of organisms into the environment is prohibited. The stipulated physical and biological containment ensures that this research will proceed with a high degree of safety and precaution.

With a view to promoting public understanding of its issuance of the Guidelines, NIH conducted an environmental impact assessment and prepared the present draft "environmental impact statement" in accordance with the National Environmental Policy Act of 1969. Notice of the availability of this document appeared in the Federal Register of September 2.

In order to extend the opportunity for public comment and consideration, the present draft environmental impact statement is offered for general comment. The reader is referred to this draft statement to the Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments should be submitted by October 18, 1976.

Additional copies of this draft are available from Dr. Rudolf G. Wanner, Associate Director for Environmental Health and Safety, Building 12A, Room 4051, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014.

Dated: August 26, 1976.

DONALD S. FREDRICKSON,
Director,
National Institutes of Health.

DRAFT ENVIRONMENTAL IMPACT STATEMENT

GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND

August 19, 1976

GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES
National Institutes of Health, Public Health Service, DHEW, Bethesda, Maryland

(X) Draft ( ) Final Environmental Impact Statement.

Name of Action

(X) Administrative ( ) Legislative Action.

Additional Information

Additional information on the proposed action, including technical documents pertinent to this statement may be obtained from:

Dr. Donald S. Fredrickson, Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014, Telephone: (301) 496-2453.

A copy of the "Guidelines for Research Involving Recombinant DNA Molecules" is attached. (Appendix D)

COMMENTS

The Department, in issuing this draft, is requesting comments on the accuracy of the factual information (including the absence of relevant material) and the predictions contained therein. Comments shall be submitted by October 18, 1976, the Council on Environmental Quality weekly notice in the Federal Register. Address comments to Dr. Donald S. Fredrickson.

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III. Objective of the NIH Action.
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   I. Possible hazardous situations.

FEDERAL REGISTER, VOL. 41, NO. 175—THURSDAY, SEPTEMBER 9, 1976
The promise of recombinant DNA research for better understanding and improved treatment of human disease is great. There is also a possible risk that microorganisms with foreign genes might cause disease or alter the environment should they escape from the laboratory and become established as commensals or as pathogens. The possible hazards remain speculative. The Guidelines prohibit certain kinds of recombinant DNA experiments and, for those experiments that are permitted, they specify safety precautions and conditions designed to protect the health of laboratory workers, the general public, and the environment should the putative hazards prove real.

The objective of the proposed action—release of the NIH Guidelines—is the protection of laboratory workers, the general public, and the environment from infection by possibly hazardous agents that may result from recombinant DNA research. The Guidelines are meant to ensure that experiments involving recombinant DNA molecules and which are supported by NIH, are carried out under conditions and safeguards that minimize the possibility of the harmful exposure of any human being or other component of the environment to these possibly hazardous agents.

It is NIH policy that all work supported by NIH, either in its own laboratories or through grants or contracts to various organizations, must be carried out according to the Guidelines. As part of this objective, the Guidelines describe procedures that will be used to ensure implementation. A further objective of establishing the Guidelines is to influence, to the extent possible, other Federal, non-Federal, and foreign organizations in their efforts to assure that recombinant DNA experiments will be carried out with minimal risk to laboratory workers, the general public, and the environment.

IV. BACKGROUND

A. DESCRIPTION OF THE RECOMBINANT DNA EXPERIMENTAL PROCESS

All living things, from subcellular particles to higher organisms, require specific information for their reproduction and functions. The basic source of this information is deoxyribonucleic acid (DNA), which is the principal substance of the genes, the units of heredity (1). Each cell of an organism is composed of various organized structures, several of which contain DNA. Figure IV-1 illustrates a typical cell.

DNA plays two roles: (1) Provides information for the reproduction, growth, and functions of the cell, and (2) preserves and directs replication of this information and transfers it to the offspring. These two roles of DNA are common to animals, plants, single-cell organisms, and many viruses. The DNA of cells is mainly found in organized structures called chromosomes.

Intracellular DNA also occurs outside of the chromosomes as extrachromosomally replicating molecules. Such DNA molecules include the plasmids, found in bacteria; the DNA of chloroplasts, common to green plants; and the DNA of mitochondria, the energy-producing units of the cells of complex organisms. These DNAs, while not strictly part of the inherent genetic make-up of a cell, help define the cell's capability.

Another type of DNA commonly found in cells is the DNA of infecting viruses.

In the past 30 years the structure of the DNA molecule has been studied in...
much detail. The molecule may be compared to a very long, twisted step-ladder with thousands to millions of rungs (shown in Figure IV-2). The sides of the ladder are formed of sugar molecules (deoxyribose) attached end to end through phosphate groups. At right angles to each sugar molecule is one of four possible bases—adenine, guanine, thymine, and cytosine. The precise sequence of these bases, the rungs of the ladder, codes the information content. The "reading" of the code contained in the sequence of bases results in the formation of proteins which in turn permit the essential functions of the cell.

A gene is a portion of the DNA molecule which codes for the manufacture of a single protein. In higher organisms, much of the DNA may not serve as genes. In this sense, but may regulate the activity of nearby genes. It is possible to break open cells and isolate DNA, free of other cellular constituents.

In recombinant DNA experiments, DNA is first isolated from two different cell types. Each DNA is then broken into segments. Each segment may contain one or more genes, or it may contain a portion of the DNA that lacks functional genes. The breaking is accomplished by means of bacterial enzymes (restriction endonucleases) which cut the DNA in such a way that the chemical structure at the ends of the segments permits incontrovertible rejoining when the two different DNAs are mixed. In this way, single DNA molecules containing portions of the different DNAs are constructed. The DNA recombined in these experiments can be derived from widely divergent sources. The DNA from one of the sources serves as a carrier, or vector, for the insertion of the recombinant DNA into a cell, or host. The vector may be DNA from a virus or a plasmid, usually derived from the same species as will serve as the host of the recombinant DNA. From a growth culture of the host cells, those containing the DNA fragment of particular interest are selected and allowed to multiply. The resulting population of identical cells is called a "clone." In some experiments the DNA will be extracted from the cells for study; in others, the properties of the cells themselves will be investigated.

In the experiments discussed in the Guidelines, the host cells are generally single-cell microorganisms such as bacteria, or animal or plant cells that were originally obtained from living tissue but are grown in single cells under special laboratory conditions.

The process of producing recombinant DNA molecules and introducing them into cells is illustrated in Figure IV-3.

**Figure IV-3**

The cell represented at the upper left contains chromosomal DNA and several separately replicating DNA molecules. The non-chromosomal DNA molecules can be isolated from the cell and manipulated to serve as vectors (carriers) for DNA from a foreign cell or from DNA molecules used as vectors. They can be cleaved, as shown, by enzymes (restriction endonucleases) to yield linear molecules with rejoined ends. At the upper right is another cell, represented here as a rectangle. It serves as the source of the foreign DNA to be inserted in the vector. This DNA can also be cleaved by enzymes. The rectangular cell could be derived from any living species, and the foreign DNA might contain chromosomal or non-chromosomal DNA, or both.

In the next steps, the foreign DNA fragment is mixed and combined with the vector DNA, and the recombinant DNA is reinserted into a host cell. In most experiments this host cell will be of the same species as the source of the vector. The recipient cells are then placed under conditions where they grow and multiply by division. Each new cell will contain recombinant DNA.

**B. EVENTS LEADING TO DEVELOPMENT OF GUIDELINES**

On June 23, 1976, the Director, NIH, released "National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules" (see Appendix D). This action was approved by the Secretary of Health, Education, and Welfare and the Assistant Secretary for Health. The Guidelines established carefully controlled conditions for the conduct of experiments involving the insertion of recombinant genes into organisms, such as bacteria. The chronology leading to the present Guidelines and the decision to release them are outlined below.

It was some of the scientists engaged in recombinant DNA experiments who called for a moratorium on certain kinds of experiments in order to assess the risks and devise appropriate guidelines. The capability to perform DNA recombination and the potential hazards, had become apparent at the Gordon Research Conference on Nucleic Acids in July 1974. Those in attendance voted to send an open letter to Dr. Philip Handler, President of the National Academy of Sciences, and to Dr. John R. Horness, President of the National Academy of NAS. The letter, appearing in "Science" (2), suggested that the Academy "establish a study committee to consider this problem and to recommend specifications or guidelines, that should seem appropriate."

In response, NAS formed a committee, and its members published another letter in "Science" in July 1974 (3). Under the title "Potential Biohazards of Recombinant DNA Molecules," the letter proposed:

First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with the members of this committee in voluntarily deferring [cert certain] experiments.

Second, plans to link fragments of animal DNAs to bacterial plasmid DNA or bacteriophage DNA should be carefully weighed.

Third, the Director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (1) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules; (2) developing procedures which will minimize the spread of such molecules within human and other populations; and (3) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

On October 7, 1974, the NIH Recombinant DNA Molecule Program Advisory Committee (hereafter "Recombinant DNA Advisory Committee") was established to advise the Secretary of HEW, the Assistant Secretary for Health, and the Director of NIH concerning a program for developing procedures which will minimize the spread of such molecules within human and other populations, and for devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

The international meeting, proposed in the "Science" article (2) was held in February 1975 at the Asilomar Conference Center, Pacific Grove, California. It was sponsored by the National Academy of Sciences and supported by the National Institutes of Health and the National Science Foundation. One hundred and fifty persons, including foreign scientists from 15 countries, 16 representatives of the press, and 4 attorneys.

The conference reviewed progress in research on recombinant DNA molecules and discussed ways to deal with the potential biohazards of the work. Participants felt that experiments on-
construction of recombinant DNA molecules should proceed: Provided, that appropriate containment is utilized. The conference made recommendations for matching levels of containment with levels of possible hazard for various types of experiments. Certain experiments were judged to pose such serious potential dangers that the conference recommended against their being conducted at the present time.

A report on the conference was submitted to the Assembly of Life Sciences, National Research Council, NAS, and approved by its Executive Committee on May 20, 1975. A summary statement of the report (4) was published in "Science, Nature," and the "Proceedings of the National Academy of Sciences." The report noted that "in many countries steps are already being taken by national bodies to formulate codes of practice for the conduct of experiments with known or potential biohazards. Until these are established, we urge individual scientists to use the proposals in this document as a guide.

The Recombinant DNA Advisory Committee held its first meeting in San Francisco immediately after the Asilomar conference. It proposed that NIH use the recommendations of the Asilomar conference for research by NIH in the United States and reviewed a proposed NIH contract program for the construction and testing of microorganisms that would result in any advantage to the organism, and that decreases the probability of harmful effects will decrease. It is unlikely that uncontrolled, and can be switched on and off as needed. It is unlikely that uncontrolled, nonessential properties such as might be introduced by foreign genes would result in any advantage to the

1. Possible hazardous situations. The stable insertion of DNA derived from a different species into a cell or virus (and therefore the progeny thereof) may change certain properties of the host. The changes may be advantageous, detrimental, or neutral with regard to (a) the survival of the recipient species, (b) other forms of life that come in contact with the recipient and (c) aspects of the nonliving environment. Current knowledge does not permit accurate assessment of whether such changes will be advantageous, detrimental or neutral, and that decrease by an order of magnitude the likely hazards of the particular recombinant DNA experiment.

The following discussion is speculative and consider ways in which hazardous agents might be produced.

a. The effect of foreign DNA on the survival of recipient species (host cells or viruses). The effect of foreign DNA on the survival of recipient species is important to the discussion of possible hazards of recombinant DNA experiments because although a recipient species may acquire a potential for harmful effects as a result of the foreign DNA, the possibility that the harmful effect will occur will depend on the survival of the recipient and its ability to multiply. If acquisition of foreign DNA increases the probability of survival and multiplication the possibility of harmful effects will increase. Similarly, if acquisition of foreign DNA decreases the probability of survival or multiplication, the possibility of harmful effects will decrease. It is important to recognize that the potential for harmful effects, that significant infections of animals and plants by bacteria or viruses may require contact with either a large or small number of the infectious agent, depending on the agent.

There are various indications that bacteria and viruses containing inserted foreign DNA are less likely to survive and multiply than are the original organisms. Natural evolution results in the survival of well-balanced and efficient organisms. Examples include the function of a cell or virus which have been lost or controlled, and can be switched on and off as needed. It is unlikely that uncontrolled, nonessential properties such as might be introduced by foreign genes would result in any advantage to the survival and multiplication of an other.
wise well-balanced organisms. It is more likely that the new properties accompanying insertion in foreign DNA will confer some relative disability to the recipient organisms. Therefore it is likely that bacterial cells containing inserted foreign DNA will multiply more slowly than the same cells without foreign DNA. Thus, in a natural competitive environment, bacteria containing recombinant DNA would generally be expected to disappear. The rate at which this occurs will depend on the relative rate of growth compared to other, competing bacteria. The following calculation demonstrates this point.

Assume that a new organism constitutes 0.001 percent of a population, but grows 10 percent less rapidly than its natural counterpart. The new organism will drop from a concentration of 0.001 percent to a concentration of 0.0001 percent (1 part in 1,000,000) in 207 generations. If the generation time of the natural organism is one hour, this amounts to about 6.5 days.

One example of a situation in which the capability of recipient bacterial host cells to survive may be significantly increased as the result of the presence of a foreign DNA of resistance to antibiotics and drugs. It is well known that such resistance is often genetically determined and genes specifying resistance have been described. Further, it is well known that such genes may be transferred, by natural DNA recombination, from one species of microorganism to another. Such natural events are in fact responsible for the rapid and widespread resistance to clinically important drugs that has been observed during the last 20 years.

The ability of recipient bacterial host cells to survive and multiply may also be enhanced by acquisition and expression of a foreign gene conferring the ability to metabolize particular nutrients. In such an environment containing the metabolite, such a recombinant might compete successfully against organisms native to the niche. This could result in destruction of an environmental competitor and the establishment of the new niche. Also, if the native organisms were performing beneficial functions, those functions could be lost upon the successful establishment of the recombinant in the niche.

The effect of bacteria and viruses containing recombinant DNA on other forms of life. The analysis leading to the Guidelines centered on the possibility of deleterious effects, since the concern was the health and safety of living organisms, including humans, and the environment. Agents constructed by recombinant DNA technology could be hazardous to other forms of life by becoming pathogenic (disease-producing) or toxigenic (toxin-producing), or by becoming more pathogenic or toxigenic than the original agent.

There are two basic mechanisms by which a recipient microorganism might be altered with regard to its pathogenicity or toxigenicity. As a result of a resident recombinant:

1. The recombinant DNA may result in formation of a protein that has undesirable effects. The case in which bacterial cells are used as carriers of foreign DNA is discussed first. A foreign protein, specified by the recombinant DNA, might not after being liberated from the microorganism, or it could function within the microorganism and alter, secondarily, normal microbial cell function in such a way that the cell is rendered harmless to other living things. Either means depends on the expression of the foreign genes; that is, the information in the foreign gene is transferred to the bacterial machinery to produce a foreign protein. Examples of proteins that might prove harmful to other organisms are hormones, enzymes.

2. The weight of present evidence suggests that foreign DNA from bacteria of one species, when inserted into bacteria of another species, may be expressed in the recipient. For example, if the donor of the foreign DNA produces a toxic substance, then the recipient cell may produce such a substance if the gene for that toxic substance is present in the recombinant. The recipient may or may not be more hazardous than the original donor organism, depending on the relative ability of the two organisms to grow and infect an animal or plant species at risk.

The evidence available at present is insufficient to predict whether or not foreign genes derived from a complex organism (animals, plants, yeasts, and fungi) will be expressed in a bacterium in any particular instance. It may be that specific manipulations will be required to permit bacteria to express information of a foreign DNA efficiently. Faithful expression of a gene requires accurate functioning of the complex bacterial machinery involved in protein synthesis. At each step, specific signals originating in the foreign gene must be recognized by the bacterial machinery. Evolutionary divergence has resulted in different signals in bacteria and complex organisms.

Attempts to translate animal virus and animal cell genes into protein, using cell-free systems containing the protein-synthesizing machinery isolated from bacteria such as E. coli yield some protein-like products. The protein products characterized to date were not faithful products of the information in the genes.

In a few cases, intact bacteria containing recombinant genes from complex organisms have been tested for evidence of expression of the inserted gene. By and large, the expression of the genes has not yet been demonstrated, although it may occur at a low frequency. In some instances, a new protein has been found, one encoded by a bacterial gene. This result is expected if a bacterial gene is interrupted by insertion of the new DNA sequence within it, and does not necessarily indicate expression of the foreign gene. Foreign DNA from yeast have been inserted into a strain of the bacterium E. coli which cannot manufacture the amino acid histidine (9). Expression of the foreign genes results in the production of essential proteins and therefore is required for the growth of all organisms. After insertion, some cells no longer required histidine; thus, the presence of the yeast DNA overcame the requirement for histidine. This is the first suggestion that a foreign gene from an organism more complex than bacteria can actually function in a bacterial cell. (Although yeast is a single-cell organism, it contains an organized nucleus like cells of higher organisms.) Further investigation is required to explain this observation.

Analogous issues must be considered for the case in which animal viruses are the source of foreign DNA. Many viruses are simple organisms described as DNA molecules enclosed and protected by coats of protein molecules. The protein coat protects the DNA from environmental effects, thus increasing the chance of insertion of the DNA to infect a cell. If viral DNAs are recombined with foreign DNAs in such a way that necessary viral genes remain intact, then the recombinant DNA may in turn be able to produce, and be packaged in, the coat of the virus. Inadvertent dispersal of such a viral particle outside of the laboratory might then result in entry of the recombinant DNA into cells of living organisms. The foreign genes may be expressed, resulting in the formation of a protein foreign to the infected organism as well as its location in the viral DNA used as vector. Currently, few if any relevant experimental data are available so that estimates of the probability of expression are, in these instances, impossible.

(3) The recombinant DNA may itself cause pathogenic or toxie effects. Foreign DNA inserted in a bacterial gene might so alter the microbial cell's properties that it becomes harmful to other organisms. This might happen, for example, through a change in the growth rate and competitive advantage of the recipient microbial cell, resulting in increased virulence of a mildly pathogenic bacteria. In general, one would expect the inserted DNA to result in a selective advantage to the recipient organism, and a selective disadvantage to the organism, as discussed in "a" above. Similar issues arise where animal viruses serve as carriers of foreign DNA.

It is also necessary to consider situations in which DNA molecules themselves may escape from the laboratory or from the experimental host cell and enter cells of living organisms with which they come in contact. Although free DNA molecules are themselves relatively fragile (and the probability that they would survive, in a significant form or for a significant time, in air, water, or any other medium, is considered remote), they can be protected in nature in a variety of ways and be released either into, or close to, a living cell.

When a cell or virus dies, or comes close to or invades the tissue of another living organism, the recombinant DNA may effectively enter a new cell. A hazardous situation similar to that described above might ensue if foreign proteins were manufactured in this "secondary" recipient. The recombinant DNA might survive as an independent cellular component, or it could recombine by natural
process with the DNA of the secondary recipient. Various possible deleterious consequences such as a recombination may be considered.

If the secondary recipient is another microorganism, the same considerations described in IV-C-1-a apply. If the secondary recipient is one of the cells of an animal or plant, different considerations apply. The latter include alterations of normal cellular control mechanisms, synthesis of endogenous viral proteins, and insertion of genes involved in cancer production (if, for example, the foreign DNA were derived from a cancer-producing virus).

It should be pointed out that the likelihood of causing inheritable changes in the offspring of complex organisms by such a mechanism is extremely low in animals because of the protection afforded germ-line cells (eggs and sperm) by their location. Thus, the possibility that recombined foreign DNA would reach germ line cells at a time in the life of such cells when secondary recombination can occur is extremely remote. With one-celled organisms, plants, or simple multicellular organisms, the probability of causing inheritable change by secondary recombination may be higher.

What is the probability of secondary recombination between prokaryotes and eukaryotes in nature? It is generally held that recombination in nature is more likely if similar or identical sequences of bases (runs in the DNA ladder) occur in the two recombining DNAs. The greater the degree of similar sequences, the more likely is recombination. In general, the more closely two species are related, the more likely it is that similar sequences will be found in their DNAs. Thus, DNA from primates has more DNA sequences in common with human DNA than does DNA from mice, or fish, or plants. Recombination may also occur between DNAs not sharing sequences but at lower frequencies.

It is possible that the capacity for interspecies recombination between distantly related organisms also exists in nature. For example, bacteria in animal intestines are constantly exposed to fragments of animal DNA released from dead intestinal cells. Recombination requires the uptake of intact segments of animal DNA and their subsequent incorporation into the bacterial DNA. The frequency of such events is unknown.

There are very few available data permitting assessment of the reverse process—namely, the incorporation of bacterial DNA into the cells, or DNA of more complex organisms. Unfortunately, reports of experiments in which bacterial DNA was inserted into animal and plant species and production of the bacterial protein followed, the process is very inefficient and many investigators have been unable to repeat these experiments (6-8).

There are certain well-documented instances of DNA of different living things becoming more or less permanently recombined in nature. These instances involve recombination between the DNAs of nonchromosomal genes, such as those of viruses or plasmids, or recombination between the DNAs of viruses and cellular genes. The former instance, for example, is the mechanism behind the rapid spread of resistance to antibiotics among different bacterial species (9, 10). This spread occurred in highly related bacteria. This is probably also the predominant use of antibiotics in medicine and agriculture. Some viral DNAs recombine into and persist in, chromosomal DNA of cells of recipient species as eukaryotic DNAs acquire, in stable form, DNA sequences derived from their host cells (13, 14). There is also strong evidence for recombination of the DNA of RNA tumor viruses with chromosomal genes (15-17).

2. Expected benefits of DNA recombinant research. Benefits may be divided into two broad categories: An increased understanding of basic biological processes, and practical applications for medicine, agriculture, and industry.

At this time the practical applications are of little importance. It is important to stress that the most significant results of this work, as with any truly innovative endeavor, are likely to arise from this unique perspective and perhaps not follow a predictable path.

a. Increased understanding of basic biological processes. There are many important fundamental biomedical questions that can be answered or approached by DNA recombinant research. In order to advance against diseases in inheritance, we need to understand the structure of genes and how they work. The DNA recombinant methodology provides a simple and inexpensive way to prepare large quantities of specific genetic information in pure form. This should permit elucidation of the organization and function of the genetic information in higher organisms. For example, current estimates of the fraction of this information that codes for proteins are simply educated guesses. There are almost no clues about the function of the portions of DNA that do not code for proteins, although these DNA sequences are suspected of being involved in the regulation of gene expression.

The existing state of ignorance is largely attributable to our previous inability to isolate discrete segments of the DNA in a form that permits detailed molecular analysis. Recombinant DNA methodology remove this barrier. Furthermore, ancillary techniques have been developed whereby pure DNA segments that contain particular sequences of interest can be identified and selected. Of particular interest is the isolation of pure DNA segments that contain the genes which are desirable and the portions of the immunoglobulin proteins. The analyses of such segments obtained from both germline and somatic cells should be of insuperable value in determining the mechanism of immunologic diversity.

A major problem in understanding the mechanism by which certain viruses cause cancer is how and where the integrated or endogenous genes are integrated into the cell's chromosome. This bears on the question of how the expression of the integrated viral genes affects cellular regulation, thus leading to the abnormal growth characteristics of cancer cells. With the recombinant DNA techniques for isolation and purification of specific genes, this research problem is reduced to manageable proportions. It is possible to isolate the desired DNA segment in pure form. Large quantities can be obtained for detailed study by simply extracting a culture of the bacteria carrying the viral DNA segment.

b. Potential practical applications for medicine, agriculture and industry. Certain of the potential applications will only be realized if the recombination of the recombinant foreign DNA in a recipient host cell is followed by expression of the genetic information contained in the DNA in the form of synthesis of proteins. Since the efficient translation of eukaryote genes in bacterial (prokaryote) hosts has yet to be proved, these potential applications are speculative at this time. Applications that depend on expression of the desired material of eukaryotic or prokaryotic DNA in prokaryote recipient cells are presently more certain.

(1) Synthesis of medically important proteins and other substances. It has been suggested that genes coding for medically important substances be attached to bacterial vectors, and that the bacteria then be used to produce large quantities of the desired material. A number of costly and/or rare substances would be prime candidates for such synthesis:

Human insulin (a future shortage of currently used animal insulin appears to be likely);

Human growth hormone (presently available only from human endeavors and in short supply);

Clothing factor VIII (for treatment of hemophilia);

Specific antibodies and antigens (for preventing and treating infectious, allergic, and autoimmune diseases, and perhaps even cancer);

Certain enzymes, such as thrombin and urokinase (promising agents in the treatment of embolism and lysosomal enzymes).

(2) Endowment of plants with new capabilities. Whole-plant species may be generated from a single cell, and thus insertion of recombinant DNA into such cells might make it possible to endow plant species with the capability of—

Improved photosynthetic fixation of carbon dioxide;

Nitrogen fixation by presently insect species (thereby reducing the need for costly chemical fertilizers that cause pollution—e.g., eutrophication);

Producing a higher quality or quantity of food protein.

(3) Some industrial applications. A number of industrial processes utilize microorganisms containing enzymes (which are proteins) to produce important chemicals (e.g., steroid hormones or other drugs, vitamins) or foodstuffs (e.g., cheese). Such processes could be improved through innovations effected by DNA recombinant research. Completely new biosynthetic reactions may thereby become available, permitting the synthesis of large amounts of complex and...
valuable compounds with ease and at low cost.

Some highly speculative applications relate to the area of energy production and neutralization of pollutants—e.g., as in oil spills. Genetic modification through DNA recombination might be possible to devise microorganisms tailor-made for such tasks in the future. The experiments primarily involve insertion of low valuable compounds with ease and at low cost.

3. Long-range implications. The experimental situations treated in the Guidelines are those that appear feasible either currently or in the near future. The experiments primarily involve insertion of recombinant DNA into bacteria or into single cells derived from more complex organisms and maintained under special laboratory conditions. It is only in the case of plants that the Guidelines cover experiments involving insertion of DNA into cells capable of developing into complex, multicellular organisms. The Guidelines and the discussions leading to their development have focused on problems of safety.

It is possible that techniques similar to or derived from recombinant DNA methodology may, in the future, be applicable to the deliberate modification of complex animals, including humans. Such modification might have as its aim combating inherited defects in an individual, or alteration of heritable characteristics in the offspring of individuals of a given species. The latter type of alteration has been successfully achieved in agriculture for centuries, by classical breeding techniques. It may be that recombinant DNA methods, should they develop in appropriate ways, may offer new opportunities for specificity and accuracy in animal breeding.

The deliberate application of such methods for the correction of individual genetic defects or the alteration of heritable characteristics in man raises complex and difficult problems. In addition to philosophical, moral, and ethical questions of concern to individuals, serious socio-economic and political issues raise their heads. Discussion of these problems in a variety of fora will be required to inform both private and public decision-making.

4. Possibility of escape. In the event that recombinant DNA technology can yield hazardous agents, such agents might be considered for deliberate perpetration of harm to animals (including humans), plants, or the environment. The possibilities include biological warfare or sabotage. Because it is not known whether recombinant DNA technology can yield such agents, discussion of these problems such as the possibility of sabotage is hypothetical and difficult. With regard to biological warfare, a July 3, 1975 letter to Dr. David Baltimore from James L. Malone, General Counsel of the United States Arms Control and Disarmament Agency says, “you raise the question as to whether the Biological Weapons Convention proscribes production of recombinant DNA molecules for purposes of constructing biological weapons. In our opinion the answer is in the affirmative. The use of recombinant DNA molecules for such purposes clearly falls within the scope of the Convention’s prohibition.”

NOTICES

References


V. DESCRIPTION OF THE PROPOSED ACTION

The Director, National Institutes of Health, has issued Guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules. The Guidelines will apply to all NIH-supported research in recombinant DNA molecules— that is, molecules which are made by combining segments of DNA from different organisms in a cell free system and which can be inserted into some living cell, there to replicate. The objective of the Guidelines is the protection of the laboratory worker, the general public, and the environment from infection by hazardous agents that may result from this research. The complete text of the Guidelines is found in the Federal Register, Part II, for Wednesday, July 1, 1976. As an integral part of this document, the Environmental Protection Agency says, “you raise the question as to whether recombinant DNA molecules, (7) the criteria for matching the assessed possible dangerous individual experiments with low, medium, and high hazard to man and other living things. These correspond to the terms Minimal, Moderate, and High, respectively, as used in the NIH Guidelines. The safeguards include usual and special microbiological safety practices, primary physical barriers that isolate the experiment from the laboratory worker, and facility installations that either markedly reduce or eliminate the potential for accidental dissemination of recombinant DNA molecules to the environment. The four levels, designated P1 to P4, provide increasing protection against contact with or accidental release of microorganisms containing recombinant DNA molecules.

Additional safeguards are provided by the use of host cells and vectors with demonstrably limited ability to survive in other than specially designed laboratory environments. This concept is called “biological containment” in the Guidelines. In the case of bacterial host cells and vectors, this means that particular strains of cells and vectors with genetically determined and fastidious survival requirements must be used. For those experiments judged to be of potentially moderate or high risk, the properties of the bacterial strains to be used
must be certified by the NIH Recombinant Advisory Committee prior to initiation of the experiment. In the case of a vector derived from an animal virus, the virus itself must be a low risk agent (CDC or National Cancer Institute), and a strain of host cells that does not transmit infection must serve as the source of the vector DNA.

The selection of containment (safeguard) levels is dependent on the assessed dangers of particular experiments involving recombinant DNA molecules. In the absence of evidence of any hazard actually occurring, these standards are based on relevant current knowledge. Permissible experiments are placed into four classes of increasing possible danger which correspond to the four levels of increasing containment capability (safeguards). Certain experiments, judged to have the potential for extreme hazard, should they prove dangerous, are prohibited.

The possibility for danger depends on:

1. The biohazard associated with the DNA of the cell or microorganism that serves as the DNA source (e.g., genes for toxic production),
2. The degree to which the DNA segment has been purged away from other genes and shown to be free of harmful characteristics,
3. The biohazard associated with the vector that serves to transmit the source DNA to a recipient host cell,
4. The ability of the vector to survive in natural environments or habitats,
5. The kinds and number of different organisms that are susceptible to infection by the recipient or vector,
6. The biohazard of the recipient host cell that serves to replicate the recombinant DNA molecule,
7. The ability of the recipient cell to survive in natural environments or habitats,
8. The ability of the recipient cell to transmit the recombinant DNA molecule to other cells capable of surviving in natural environments or habitats,
9. The potential of the recipient cell to obtain the source DNA by natural means, and
10. The evolutionary relatedness of the DNA source to humans.

The Guidelines prohibit a number of types of experiments including those in which an organism contributing DNA is itself a biohazard of greater than low risk as determined by conventional methods of risk assessment (low risk corresponds to class 2 agents as defined by the Center for Disease Control). The host cells and vectors are required to be of no or minimal risk. The potential dangers and safeguards to increase as the organism providing the source DNA approaches humans phylogenetically. Thus, source DNA from primate cells is considered to have greater potential dangers than source DNA from lower eukaryotes. In general, greater possible dangers are assigned to recombinants that are present in the most hazardous containment level designed to construct the DNA.

The risk-assessment standards are patterns of the building, and public access to potentially harmful organisms. These standards are based on relevant current knowledge. Permissible experiments are placed into four classes of increasing possible danger which correspond to the four levels of increasing containment capability (safeguards). Certain experiments, judged to have the potential for extreme hazard, should they prove dangerous, are prohibited.

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1. The biohazard associated with the DNA of the cell or microorganism that serves as the DNA source (e.g., genes for toxic production),
2. The degree to which the DNA segment has been purged away from other genes and shown to be free of harmful characteristics,
3. The biohazard associated with the vector that serves to transmit the source DNA to a recipient host cell,
4. The ability of the vector to survive in natural environments or habitats,
5. The kinds and number of different organisms that are susceptible to infection by the recipient or vector,
6. The biohazard of the recipient host cell that serves to replicate the recombinant DNA molecule,
7. The ability of the recipient cell to survive in natural environments or habitats,
8. The ability of the recipient cell to transmit the recombinant DNA molecule to other cells capable of surviving in natural environments or habitats,
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10. The evolutionary relatedness of the DNA source to humans.

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1. The biohazard associated with the DNA of the cell or microorganism that serves as the DNA source (e.g., genes for toxic production),
2. The degree to which the DNA segment has been purged away from other genes and shown to be free of harmful characteristics,
3. The biohazard associated with the vector that serves to transmit the source DNA to a recipient host cell,
4. The ability of the vector to survive in natural environments or habitats,
5. The kinds and number of different organisms that are susceptible to infection by the recipient or vector,
6. The biohazard of the recipient host cell that serves to replicate the recombinant DNA molecule,
7. The ability of the recipient cell to survive in natural environments or habitats,
8. The ability of the recipient cell to transmit the recombinant DNA molecule to other cells capable of surviving in natural environments or habitats,
9. The potential of the recipient cell to obtain the source DNA by natural means, and
10. The evolutionary relatedness of the DNA source to humans.

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2. The degree to which the DNA segment has been purged away from other genes and shown to be free of harmful characteristics,
3. The biohazard associated with the vector that serves to transmit the source DNA to a recipient host cell,
4. The ability of the vector to survive in natural environments or habitats,
5. The kinds and number of different organisms that are susceptible to infection by the recipient or vector,
6. The biohazard of the recipient host cell that serves to replicate the recombinant DNA molecule,
7. The ability of the recipient cell to survive in natural environments or habitats,
8. The ability of the recipient cell to transmit the recombinant DNA molecule to other cells capable of surviving in natural environments or habitats,
9. The potential of the recipient cell to obtain the source DNA by natural means, and
10. The evolutionary relatedness of the DNA source to humans.

The Guidelines prohibit a number of types of experiments including those in which an organism contributing DNA is itself a biohazard of greater than low risk as determined by conventional methods of risk assessment (low risk corresponds to class 2 agents as defined by the Center for Disease Control). The host cells and vectors are required to be of no or minimal risk. The potential dangers and safeguards to increase as the organism providing the source DNA approaches humans phylogenetically. Thus, source DNA from primate cells is considered to have greater potential dangers than source DNA from lower eukaryotes. In general, greater possible dangers are assigned to recombinants that are present in the most hazardous containment level designed to construct the DNA.

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3. The biohazard associated with the vector that serves to transmit the source DNA to a recipient host cell,
4. The ability of the vector to survive in natural environments or habitats,
5. The kinds and number of different organisms that are susceptible to infection by the recipient or vector,
6. The biohazard of the recipient host cell that serves to replicate the recombinant DNA molecule,
7. The ability of the recipient cell to survive in natural environments or habitats,
8. The ability of the recipient cell to transmit the recombinant DNA molecule to other cells capable of surviving in natural environments or habitats,
9. The potential of the recipient cell to obtain the source DNA by natural means, and
10. The evolutionary relatedness of the DNA source to humans.
brian tos, and ceilings are easily cleanable to facilitate housekeeping and space decontamination. The laboratory ventilation system is balanced to provide for an inflow of supply air from the access corridor into the laboratory. No work in open vessels is conducted on the open bench; all such procedures are confined to biological safety cabinets.

P4 Level (High). As shown in Figure V-4, experiments involving recombinant DNA molecules requiring physical containment at the P4 level shall be confined to work areas in a maximum-security facility of the type designed to contain microorganisms that are extremely hazardous to man or may cause serious epidemic disease. The facility is either a separate building or a controlled interior area completely isolated from all other areas of a building. Access to the facility is under strict control. Class III biological safety cabinets are available.

A P4 facility has engineering features, shown in Figure V-5, designed to prevent the escape of microorganisms to the environment (1-4). The special features in a P4 facility include:

- Monolithic walls, floors, and ceilings in which all penetrations such as for air ducts, electrical conduits, and utility pipes are sealed to ensure the physical isolation of the work area and to facilitate housekeeping and space decontamination.
- Air looks through which supplies and materials can be brought safely into the facility.
- A separate treatment system to sterilize liquid effluents from the facility.
- Furnace and space decontamination.
- Electrical conduits, and utility pipes are sealed to ensure the physical isolation of the work area.
- Double-door autoclaves to sterilize biowaste treatment system to sterilize DNA molecules requiring physical containment at the P4 level shall be confined to work areas in a maximum-security facility of the type designed to contain microorganisms that are extremely hazardous to man or may cause serious epidemic disease. The facility is either a separate building or a controlled interior area completely isolated from all other areas of a building. Access to the facility is under strict control. Class III biological safety cabinets are available.

When that the time only restrictions on recombinant DNA research stemmed from voluntary compliance of the research community with the guidelines developed at the International Conference on Recombinant DNA Molecules, held at Asilomar, California, in February of 1975, which were published in scientific journals. The Asilomar guidelines differ in substance from the NIH Guidelines, and are considerably less stringent and less detailed in their requirements for containment of potentially hazardous organisms. For example, experiments that may be carried out with minimal containment according to the specific language of the Asilomar guidelines, the construction of an E. coli plasmid containing the noncancer-producing DNA element of SV40) require P3 or P4 according to the NIH Guidance.

REFERENCES


VI. DESCRIPTION OF ALTERNATIVES

The following general classes of action have been considered as alternatives to, or in addition to, the proposed action. The impact of each is described briefly, and reference is made to other portions of this document which have a more complete discussion of the particular impact in question.

A. NO ACTION

This alternative would perpetuate the situation existing prior to June 30, 1976. At that time the only restrictions on recombinant DNA research stemmed from voluntary compliance of the research community with the guidelines developed at the International Conference on Recombinant DNA Molecules, held at Asilomar, California, in February of 1975, which were published in scientific journals. The Asilomar guidelines differ in substance from the NIH Guidelines, and are considerably less stringent and less detailed in their requirements for containment of potentially hazardous organisms. For example, experiments that may be carried out with minimal containment according to the specific language of the Asilomar guidelines, the construction of an E. coli plasmid containing the noncancer-producing DNA segment of SV40) require P3 or P4 according to the NIH Guidelines. In addition, while the Asilomar guidelines recommend that certain experiments be deferred, the list of experiments to be deferred is expanded in the NIH Guidelines. Furthermore, disregard of the Asilomar guidelines carries no sanctions on investigators, and it could be expected that the currently high level of voluntary compliance would be eroded with time.

The "no action" alternative would greatly increase the probability that possibly hazardous microorganisms would be released into the environment. Public concern would be increased in the absence of any Federal action. It is concluded that the "no action" alternative would not afford adequate protection of laboratory workers, the general public, and the environment from the possible hazards described in section IV-C-1.

The alternative of "no action" would essentially remove from the conduct of research the restrictions inherent in the NIH Guidelines. Experiments concerning basic biological processes, and the development of technology applicable to medical, agricultural, and industrial problems, would proceed at a faster rate. Moreover, the immediate cost of conducting research would be increased with the "no action" alternative, since the need for costly physical containment would be less.

B. NIH PROHIBITION OF FUNDING OF ALL EXPERIMENTS WITH RECOMBINANT DNA

NIH could refuse to fund any recombinant DNA experiments. This would not necessarily result in the cessation of such research, since it may still be supported by non-NIH funds both in this country and abroad. Therefore a reduction of risks but not elimination of risks might be achieved by total NIH prohibition. Because the NIH funds a large proportion of the total biomedical research effort, a significant delay might be expected in the achievement of the goals and missions of programs designed to elucidate basic biological processes and, in turn, the mechanisms underlying various disease states. It is widely anticipated that a variety of research impacting on health and other areas of human concern—will benefit from recombinant DNA technology (see Section IV-C-2).

American scientists have played a leading role in bringing the potential hazards of recombinant DNA research to the attention of scientists, governments, and international organizations. As a result, there is an effort to adopt safety procedures for the conduct of this research in many countries. Although nations differ in their perceptions of the need to adopt safety measures, and of what the exact measures should be, the NIH Guidelines are being used as a model. NIH prohibition of the work would undermine American leadership in the establishment of worldwide standards for safety.

Finally, prohibition would be likely to be an important impact on science, both in research and in development of technology. The leadership of

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the United States in biological research would be threatened. Further, historical
precedents indicate that measures which interfere with free inquiry in areas of interest, often inhibit the vitality of other aspects of society.

C. DEVELOPMENT OF DIFFERENT GUIDELINES

Each of the stipulations in the NIH Guidelines was made after assessment of the possible hazards associated with particular experiments. The available data, however, were limited, and different conclusions could have been reached. Some issues addressed in the preparation of the Guidelines which could have led to different regulatory actions as follows:

1. Levels of physical containment. For certain experiments in which the potential risk is controversial, the physical containment level could have been higher or lower. Examples of controversial issues are the recommendations with respect to containment levels for recombinant experiments involving bacterial cells. Establishment of regional centers would have been required in one area as for other organisms.

2. Establishment of a few national P3 facilities openly available to all investigators, with the requirement that all experiments requiring P3 containment be conducted therein. In effect, this will be the situation with respect to P4 facilities under the Guidelines. There are several advantages to working in regional centers:

a. It would be less expensive to construct and staff a few such regional centers than many such facilities.

b. The sites could be centralized.

c. P3 facilities would be more uniformly accessible to qualified investigators from a variety of institutions.

d. There would be greater assurance that the facilities meet the specified requirements.

e. Banks of cells containing recombinant DNA could be maintained, with a view to decreasing the number of times the actual recombinant process would be performed (such banks can also be maintained in the absence of centralized P3 facilities).

f. The sites could be placed away from laboratory or neighboring areas. It should in effect be discouraged. Theoretically, the most desirable bacterial recipient of recombinant DNA would be a species uniquely adapted to carefully controlled laboratory environments and unable to survive or transmit DNA to other organisms in any natural environment. This means that the bacteria should be unable to survive in normal ecological conditions in the laboratory or neighboring areas. It should be unable to colonize or survive in or on other living things, or in soil or water. In addition, these properties should not be significantly altered by the insertion into the bacterium of the recombinant DNA. The bacteria must also be able to be manipulated for successful execution of the proposed experiment.

No bacterium is known to meet all these requirements. The guidelines permit the use of various forms of a particular strain of E. coli called K12. (The forms are designated EK and EK3 in the Guidelines where they are discussed in detail.) Some of these forms already exist, others need to be constructed. Although related to other E. coli strains that do not in any way meet the described criteria nor to other organisms, these permissible strains of E. coli partially fulfill many of the criteria in the definition of the ideal strain. At present, no other bacterial species is known to meet the definition as closely as E. coli K-12 and its derivatives. In the future, other bacteria, closer to the ideal, may become known, or the properties of already known species may be shown to approach the ideal more closely than E. coli strain K12 and its derivatives, as described in the Guidelines.

3. All permissible recombinant DNA experiments be conducted in P4 facilities. This alternative implies that the level of attention among experiments. It does not recognize that certain recombinant DNA experiments are widely agreed to pose little, if any, possible hazard. It is equi

4. Experiments prohibited at this time. Certain types of experiments are prohibited by the Guidelines. Their selection was a matter of judgment, and depended on the seriousness of the possible hazard. Alternative assessments would result in either an expansion or a contraction of the list of guidelines. The consequent reduction or increase in the possible risks. Some of the controversial recommendations are:

a. The prohibition of experiments involving more than 10 liters of culture fluid containing recombinant DNAs known to make harmful products without the express approval of the NIH Recombinant Advisory Committee.

b. Sanction of the use of the bacterium Escherichia coli containing recombinant DNA molecules. This organism has been studied extensively and is well suited to recombinant DNA research. It has been argued, however, that E. coli could not be used as such time. This is because many E. coli strains are intimately associated with humans and other living things, and because they readily exchange DNA (genes) with certain other bacteria.

Theoretically, the most desirable bacterial recipient of recombinant DNA would be a species uniquely adapted to carefully controlled laboratory environments and unable to survive or transmit DNA to other organisms in any natural environment. This means that the bacteria should be unable to survive in normal ecological conditions in the laboratory or neighboring areas. It should be unable to colonize or survive in or on other living things, or in soil or water. In addition, these properties should not be significantly altered by the insertion into the bacterium of the recombinant DNA. The bacteria must also be able to be manipulated for successful execution of the proposed experiment.

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c. Sanction of the use of Simian Virus 40 (SV40) as a carrier of a foreign DNA fragment. It has been argued that SV40 should not be permitted, since it is known to cause cancer in laboratory animals. There is little evidence that SV40 results in disease in humans. However, SV40 infects humans, and demonstrate that SV40 infection has occurred in some members of the general population. Some of the infection may have resulted from the inadvertent inoculation of millions of individuals during the initial mass program of immunization against polio virus before SV40 was identified as a contaminant in the vaccine. The antibodies may have been formed against SV40-like viruses known to exist naturally in humans (1). It is possible that a recombinant DNA carried by SV40 could infect humans and signifi

4. Experiments prohibited at this time. Certain types of experiments are prohibited by the Guidelines. Their selection was a matter of judgment, and depended on the seriousness of the possible hazard. Alternative assessments would result in either an expansion or a contraction of the list of guidelines. The consequent reduction or increase in the possible risks. Some of the controversial recommendations are:

a. The prohibition of experiments involving more than 10 liters of culture fluid containing recombinant DNAs known to make harmful products without the express approval of the NIH Recombinant Advisory Committee.

b. Sanction of the use of the bacterium Escherichia coli containing recombinant DNA molecules. This organism has been studied extensively and is well suited to recombinant DNA research. It has been argued, however, that E. coli could not be used as such time. This is because many E. coli strains are intimately associated with humans and other living things, and because they readily exchange DNA (genes) with certain other bacteria.

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The disadvantages of establishing regional centers include:

a. Long-range planning would be necessary.

b. Scheduling would be a problem.

c. The investigator's independence would be diminished.

d. Competition for access might favor established investigators or established ideas.

e. The nature of the process, which might require only a brief review of P2 facilities in a given day but over a lengthy period of time.

f. Access problems might unnecessarily discourage valuable research.

3. All permissible recombinant DNA experiments be conducted in P4 facilities. This alternative implies that the level of atten

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stringent safeguards than those required by the Guidelines. The judgments of the investigator and his local committee will be reevaluated by the NIH and OSHA, reviewing the scientific merit of the proposal.

II. GENERAL FEDERAL REGULATION OF ALL SUCH RESEARCH

The NIH Guidelines control only recombinant DNA research supported by NIH. Nevertheless, NIH has assumed a real responsibility toward the promulgation of safety measures for all such research. Nationally, NIH has conducted and is continuing to conduct meetings with representatives of other Federal agencies and of private industry. In the case of the Federal Government, consideration is being given to the imposition of the Guidelines either by individual agency adoption or through an Executive Order. Non-Federal groups have indicated that they will voluntarily comply with reasonable guidelines designed to be applicable to their specific needs.

From the international standpoint, the NIH has been in communication with the World Health Organization, the National Institutes of Health, the Center for Disease Control (CDC), the International Council of Scientific Unions, and the International Council of Molecular Biology Organization, and the National Institutes of Health, among others, to encourage the widest possible application of the Guidelines.

A variety of administrative mechanisms could be employed to regulate recombinant DNA research. Relevant agencies are the Center for Disease Control (CDC), including the National Institute for Occupational Safety and Health (NIOSH), or the Occupational Safety and Health Administration, Department of Labor (OSHA). For example NIH could petition OSHA to enforce and monitor such research through its standards and enforcement mechanisms and penalties, and the NIH may establish guidelines applies to recombinant DNA research. Relevant agencies are the Center for Disease Control (CDC), including the National Institute for Occupational Safety and Health (NIOSH), or the Occupational Safety and Health Administration, Department of Labor (OSHA). For example NIH could petition OSHA to enforce and monitor such research through its standards and enforcement mechanisms and penalties, and the NIH may establish guidelines applies to recombinant DNA research.

The protection of personnel from potential dangers associated with low- and moderate-risk materials is provided by a number of safeguards, including training of the laboratory personnel from the experimental research as well as on safe microbiological practices. Potential exposure to low-risk materials through aerosols is reduced by the reduction of mechanical pipetting for low- and moderate-risk materials. Potential exposure to moderate-risk materials through aerosols is further reduced by the requirement to contain all processes that produce significant aerosols to be confined to biological safety cabinets. Potential exposure to moderate-risk materials through aerosols is further reduced by the requirement to contain all processes that produce any aerosol. The use of Class I and Class II biological safety cabinets that comply with the standards specified in the Guidelines can reduce the potential exposure by a factor of 10,000 (1). Potential exposure of laboratory personnel not involved in the handling of moderate-risk materials is further controlled by the specified laboratory access procedures. These measures do not provide absolute protection from exposures, and the required primary barriers can be compromised by lack of attention to technique, poor placement of equipment, and human error. Experience demonstrates that the use of these measures reduces but does not prevent the potential for laboratory-acquired infections with relatively infectious agents such as class 2 and class 3 agents.

The nature of the harmful effects from exposures to low- and moderate-risk recombinant DNA materials cannot be determined. However, the nature for these materials to cause disease or injury, should they be hazardous can be estimated by comparison of their infectivity with that of known class 2 and class 3 agents. The requirement that recipient bacterial cells be class 1 agents (nonpathogenic) and that animal virus vectors be similarly low risk agents (class 1) reduces the likelihood that they will have the infectious properties of class 2 or 3 agents upon insertion of foreign DNA.
Recombinant DNA experiments assessed to have high-risk potential require special precautions designed to prevent exposures, as specified in the Guidelines. All such experimental procedures are required to be conducted by the appropriate primary and secondary barriers. These are barriers that physically isolate the experimental process from the laboratory worker. Research is conducted within these barriers through attached gloves. Materials are not removed from the barriers until they have been sterilized or put into hermetically sealed containers, which are then surface sterilized.

Experience with class 3 and 4 human etiologic agents demonstrates that the absolute primary barriers can be operated without exposure of the operators under standardized procedures, employing stable, well-trained and well-disciplined personnel (2). This conclusion is based on the data in reference 2 which refer to the experience of recent years; the earlier experience is less relevant because of important recent developments in the design and availability of containment equipment. The procedures for combining DNA molecules, inserting them into recipient cells, can be standardized, and the Guidelines require that research personnel be well trained and proficient in the necessary operations. The inspection and certification of all high-risk research facilities by NIH personnel provide additional assurance that these requirements will be met.

Thus, potentially harmful effects from research with high-risk recombinant DNA molecules should be extremely unlikely given strict adherence to the NIH Guidelines.

Insofar as research sponsored by NIH is concerned, potentially harmful effects from experiments judged to present the possibility of very severe hazard should be prevented completely since these experiments are prohibited.

2. Impact on the environmental spread of possibly hazardous agents. The NIH Guidelines are directly concerned with preventing the release of cells and microorganisms containing recombinant DNA molecules, or the release of recombinant DNA molecules themselves, into the environment, thus preventing potential exposures of humans, other animals and plant communities.

The Guidelines require decontamination of all liquid and solid wastes generated by low-, moderate-, or high-risk experiments. As the potential risk of these materials increases (low → high), further measures are required to increase the minimization of their dispersal. The Guidelines recommend the decontamination of no- or minimal-risk materials before their disposal to the environment. This is standard microbiological practice.

The Guidelines prohibit the release of contaminated air under ordinary conditions. Procedures involving low- and moderate-risk materials that may produce airborne contamination are confined to primary barriers. Contaminated air from these barriers are removed by filtration.

The potential for accidental release of recombinant DNA materials into the atmosphere, however, increases with decreasing containment requirements (moderate → minimal). Harmful secondary effects from such accidental releases of low-risk materials are exceedingly remote. An analysis of 36 reported laboratory-acquired micro-epidemics in the period 1922–1976 involving over 1,000 infections with class 2, class 3, and class 4 human etiologic agents demonstrated no infections among persons who were ever in the laboratory building or who were not associated in some way with the laboratory (2). Almost all of these outbreaks occurred in the absence of genuine efforts to control contaminated air, liquid wastes, refuse, and laundry.

Any potential release of high-risk materials to the environment should be prevented by adherence to the NIH Guidelines. All high-risk materials are required to be isolated in physically contained, absolute primary barriers. All effluents from these barriers are sterilized. The barriers themselves are located in maximum-aerosol-prevention production areas that are provided with additional barriers to prevent any accidental release. Air locks, negative air pressure, clothes-change rooms, filtration and incineration of air exhaust, and secondary sterilization of all liquid and solid wastes, provide additional protection to the environment.

The NIH Guidelines also define requirements for protecting the environment from potential dangers that may be associated with the shipment of recombinant DNA materials. Federal packaging standards appropriate for the shipment of class 3 human etiologic agents are required for the shipment of all recombinant materials.

3. Cost impact. The direct cost impact of the NIH guidelines is the cost of complying with their provisions. The costs will vary according to the level of potential risk of the research. There are no special facility requirements for work with low-risk recombinant DNA materials (P1 and P2). There are equipment requirements for work involving low-risk recombinant DNA materials that will impose the greatest impact. Low-risk research requires a biological safety cabinet for procedures that may produce significant aerosols and an autoclave for sterilizing waste materials. These items of equipment, however, are generally available within the existing facilities where such research is being conducted. The cost impact of the NIH guidelines on minimum-risk research is therefore not significant.

Special equipment and facility requirements are specified for moderate-risk recombinant DNA research (P3). All work at this level of potential risk is to be conducted within biological safety cabinets (Class I or II). This requirement will necessitate the acquisition of many additional cabinets, the number being dependent on the level of the research effort. It is estimated that one cabinet will be required for every three persons involved in the research. The cost of each cabinet is approximately $6,000.

Directional air flow, single-pass ventilation, and provisions for ensuring restricted access are facility requirements specified for moderate-risk (P3) recombinant DNA research. Fewer than 30 facilities (those constructed in the last decade) have been built within this capability, few older facilities can provide this capability without extensive renovation. Creating adequate access control by construction of architectural barriers (e.g., air locks, double-door alcoves, etc.) is not expensive. However, the cost of renovation of air-handling systems to provide for single-pass, directional air flow may prevent some institutions from conducting moderate-risk research. It has been estimated that installation of air-handling systems that comply with the NIH guidelines would cost approximately $200 per square foot of space serviced by the system.

The NIH Guidelines require that high-risk (P4) recombinant DNA research be conducted only in class III biological safety cabinets (glove boxes) in maximum-security facilities. Fewer than 30 facilities within the United States have the potential for meeting the requirements specified in the Guidelines for such facilities. A smaller number may actually be available for this research. It is estimated that approximately $750,000 would be required to construct and equip a maximum-security facility having two 10-foot by 20-foot laboratory modules with class III cabinetry. This great cost is due to sophisticated mechanical support systems (e.g., negative pressure exhaust, air filtration, air waste treatment plant) and architectural barriers (e.g., clothes-change rooms, air locks, waste-staging areas, and monolithic walls, floors, and ceilings). The cost of class III cabinetry installed is approximately $300 per linear foot. In addition, the cabinetry line and the facility each require a double-door autoclave, costing a minimum of $15,000 and $65,000 respectively.

4. Secondary impacts. There are three secondary impacts which further provide for environmental protection—i.e., reduce the potential risk to the environment from recombinant DNA research:

a. Limited maximum-security containment capability. The number of facilities available to support high-risk research greatly restricts the number of such experiments that can be conducted. The reduction in the number of experiments minimizes the probability of accidents resulting in laboratory worker exposure and subsequent secondary environmental impacts.

b. Safety awareness. The safe performance of biomedical research is dependent on an awareness of the risks and on safeguards required to control the risks. Issuance of the NIH Guidelines should strengthen safety performance in general by providing safety information and methods for research personnel. Increased awareness within the laboratory worker to the potential hazards associated with recombinant DNA experiments is concerned, potentially harmful effects from experiments judged to present the possibility of very severe hazard should be prevented completely since these experiments are prohibited.

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c. Early recognition of potential hazards. The Guidelines require that the principal investigator notify NIH of any serious or extended illness or accident that may result from exposure to man or to the environment. This monitoring procedure will provide an early warning of possible unforeseen hazard. For example, if a laboratory infection from exposure to a recombinant DNA molecule is confirmed, indicating a real hazard, an increase in safeguards or cessation of experiments can be required to minimize the hazard to other investigators conducting similar studies. This upgrading will also reduce any potential for environmental effects.

B. IMPACT OF EXPERIMENTS CONDUCTED UNDER THE GUIDELINES

1. Possible undesirable impact—a. Dispersion of potentially hazardous agents. The hypothetical mechanisms by which insertion of foreign genes into cells or viruses might result in the formation of hazardous agents are described in Section IV. There is, as stated before, no known instance in which a hazardous agent has been created by recombinant DNA technology. Current knowledge permits no more than speculation that such events may be possible and an equally speculative assessment of the nature and extent of hazards that may follow upon a particular recombinant DNA experiment. This is the underlying reason that the thrust of the Guidelines is to minimize contact of organisms containing recombinant DNA with other organisms or the environment. Therefore, the following analysis of possible undesirable impacts due to dispersion of potentially hazardous agents emphasizes the likelihood of significant dispersion rather than the nature of the hazard itself. The analysis given does not apply in detail to all the possible situations, but can serve as a model for analyzing different situations.

In order that any potential hazard be realized, it is necessary that each of a number of sequential events occur. Each event in the sequence is possible only if the earlier events have occurred. The organism must—

(a) Contain foreign genes,
(b) Escape from the experimental situation,
(c) Survive after escape,
(d) Become established in an environment permitting its growth and multiplication,
(e) Contact other living organisms in a significant manner, including contact by a sufficient number of organisms to insure survival and growth and to cause infection.
(Note that the environment in (d) may be a living organism itself.)

In these cases where the detrimental effect results from the formation of a harmful protein, the organism containing the recombinant DNA must—

(f) Contain a gene for a potentially harmful protein,
(g) Be able to express the foreign gene— that is, synthesize the foreign protein,
(h) Synthesize the protein in sufficient quantity to be deleterious to the infected organism.

In those cases where the foreign DNA itself may be the cause of undesirable effects, another set of events must be considered. Insertion of foreign DNA increases the pathogenicity of the initial host cell or virus, the inserted DNA must—

(i) Impart a selective advantage for growth to the carrier of the DNA as compared with the original cell or virus,
(j) Alter the metabolism of the carrier so that it becomes disease producing.

In the case where the foreign DNA causes undesirable effects by virtue of its transfer out of the original recipient and reinsertion into cells of another species, the DNA must—

(k) Leave the original recipient without being destroyed,
(l) Survive transfer to another cell,
(m) Become associated with the other cell in a stable manner, either as an independent element or by natural recombination.

For example, in a hypothetical experiment classified as low-risk and carried out according to the requirements of the Guidelines, events (a) through (h) might be required to yield a hazardous situation. Available data assign probabilities of : 1 for (a); 10^{-6} (1 in 100) for (b); 10^{-4} (1 in 10,000) for (c); and 10^{-8} (1 in a million) for (d). Lack of any pertinent knowledge concerning events (i) through (l) would make assignment of probabilities impossible. Even assuming a probability of one for each event (e) through (h), the overall probability of a deleterious effect on a member of a species at risk in this hypothetical situation would then be the product of all probabilities (a) through (d), namely 10^{-2} (one in a trillion). This probability then needs to be compared with the number of organisms grown in liquid medium (10^{12} and 10^{13} organisms per ml). The probability will also need to be corrected for the length of time over which the experiment is to be conducted. In reality, it may frequently be difficult to assess the relevant probabilities.

It is currently impossible to assign specific probabilities for many experiments, although crude estimates can sometimes be made from knowledge of laboratory-acquired infections, from prototype experiments set up to measure bacterial or viral escape (d), and from knowledge concerning the stability of organisms and DNA. NIH is currently supporting research designed to improve the ability to evaluate certain of these probabilities.

b. Other considerations. The foregoing descriptions of the kinds of possibly hazardous situations that might arise from experiments obtained through recombinant DNA experiments must be considered in the light of certain more general issues.

(1) Monitoring for release of organisms containing recombinant DNA. Control of the spread of any agent outside of an experimental situation to laboratory workers or the outside environment is greatly assisted by adequate means for monitoring the agent in question. A pertinent example is the monitoring for spillage and spread of radiolabeled DNA. The presence of radioactive tracer is easily visualized and, if necessary, the exposure of laboratory personnel or the environment to radiation can be quantified. The situation is fundamentally analogous in the case of recombinants or viruses containing recombinant DNA. No simple general procedure exists for identifying an organism released from the laboratory against the large background level of naturally occurring or related organisms occurring naturally.

It is possible, however, to devise special pertinent procedures for detection of some of the agents used in recombinant DNA experiments. For example, development of bacterial strains, phages, or plasmids carrying readily detectable genetic traits would enable the monitoring of laboratory personnel, people working in the area, and their families for the presence of these agents. This would be analogous to the examination of drinking water, lakes, etc., for fecal contamination with enteric organisms. Given in such instances could be at levels as low as 10^{-2} (1 part in 10,000,000). The adequacy of such screening is not presently known.

Given the nature of the series of events that might characterize a hazardous situation, the time factors involved in those events become relevant. Certain possible types of organisms containing recombinant DNA might, if they escaped and if they were hazardous, be immediately perceived as such—e.g., production of toxic foreign proteins. We might therefore be aware of the potential problem soon after dispersal of the organism, and reasonable means for minimizing further dispersal could be undertaken. In other instances—e.g., a cancer-producing DNA fragment—evidence of harmful effects might not be apparent for many years. The connection between the causative organisms and the observed harmful effects could be difficult to establish. Further, dispersal of the hazardous agent might then be so widespread as to make control difficult or impossible.

(2) Natural occurrence of DNA recombination between unrelated organisms. Concern over the potential for hazard in organisms containing recombinant DNA develops from the central idea that such recombinants will be unique types of organisms, not normally arising in nature, and that their properties will therefore be unknown and unpredictable. Natural environments provide many opportunities for recombination of DNA between unrelated species, as for example, in the intestines of animals. Whether or at what frequency such recombinations may occur is not known at present, but it is probably low given the very low extent of shared base sequences that can be detected in DNAs derived from distantly related organisms. It would appear that inter- or interspecies recombinants, if they occur in nature, may have been selected against in evolution. However tests for shared base sequences are of limited sensitivity.
(3) Relating irreversibility of spread of organisms. Should organisms containing recombined DNA be dispersed into the environment, they might, depending on their fitness relative to other competing organisms and their own reproduction, and a potentially dangerous organism could then multiply and possibly spread. Such subsequent experiments would not stop the diffusion of the hazardous agent. While means to eradicate the organism might be found, as in the case of smallpox, it is also possible that such means will not be available, or that they will be available too late to prevent or stop untoward events.

As described earlier, the likelihood is that newly constructed organisms will be less fit than those occurring naturally and therefore will disappear over time.

2. Beneficial impacts of recombinant DNA research. Section IV-C-2 describes the various anticipated benefits of recombinant DNA research. As-with the possible hazards, many of the proposed benefits are speculative. Assessment of the likelihood that the benefits will be realized will depend on information acquired from future experimentation. For example, assessment of the category of anticipated benefits depends on the synthesis of foreign genes in prokaryotic cells (see IV-C-1-b) awaits additional data on the expression of the foreign genes. Should these benefits be realized, it may be expected that the cost of manufacturing certain clinically important proteins can be increased. Other clinically important proteins that are either in short supply (e.g., human growth hormone) or unavailable by existing techniques may be made readily available. Innovative approaches to immunization against infectious diseases can also be expected.

Some of the anticipated benefits appear certain. These are the benefits to be derived from an increased understanding of both basic biological processes and the mechanisms underlying a variety of disease states. Application of the restrictions imposed by the Guidelines will retard progress toward the realization of the possible benefits. In addition to the prohibitions on certain experiments, there are many permissible experiments which will need to be postponed until the requirements in the Guidelines can be met. The acquisition and installation of F3 facilities requires adequate funds, extensive planning and installation. P4 facilities are limited in number. Experiments that require hosts and vectors with demonstrably limited ability to survive in natural environments must await development of appropriate hosts and vectors, their testing, and finally their certification by the NIH Recombinant Advisory Committee. Time will also be required for the various review processes that are required.

References


Appendix A
Glossary
1. Aerosol: A colloid of liquid or solid particles suspended in a gas, usually air.
2. Antibody: A protein which is formed in the body as a result of the inoculation of an antigen.
3. Antigen: A substance which is injected into an animal causing the formation of antibodies.
4. Biohazard: An apparatus for effecting sterilization by steam under pressure. It is fitted with a gauge that automatically regulates the pressure, and therefore the degree of sterilization to which the contents are subjected.
5. Bacteriophage: A virus that infects only bacteria.
6. BCBI: Bureau, Institutes, and Divisions of NIH.
7. Biohazard: A contamination of the words biological hockey agents presenting a risk or potential risk to the well-being of man, or other animals, either directly through infection or indirectly through dissemination of the virus.
8. Biohazardous Agent: Any microbial unit capable of potentially causing a biohazard.
9. Biohazard Area: Any area (a complete operating complex, a single facility, a single room within a facility, etc.) in which work has been, or is being performed with biohazardous agents or materials.
10. Biohazard Control: Any set of equipment and procedures utilized to prevent or minimize the exposure of man and his environment to biohazardous agents or materials.
11. Biohazardous Material: Any substance which contains or potentially contains biohazardous agents or materials.
13. CDC: Center for Disease Control, United States Public Health Service, Atlanta, Georgia.
14. CDG Classification of etiologic agents on the basis of hazard: A system for evaluating the hazards associated with various etiologic agents, and classification of minimal safety conditions for their management in microbiological investigations. The basis for the Agents Classification is as follows:
15. Class 1: Agent or no or minimal hazard under ordinary conditions of handling.
16. Class 2: Agents of ordinary potential hazard. This class includes agents which may produce disease of varying degrees severity from accidental inoculation or injection or other means of contamination but which are contained by ordinary laboratory techniques.
17. Class 3: Agents involving special hazard or agents derived from outside the United States which require a federal permit for importation unless they are specified for higher classification. This class includes pathogens which require special conditions for containment.
18. Class 4: Agents that require the most stringent conditions for their containment because they are extremely hazardous to laboratory animals, may cause serious disease in man, or may cause widespread disease. This class includes Class 3 agents from outside the United States when they are contained under conditions or when certain other biological agents are conducted in the same laboratory area.
19. Class 5: Foreign animal pathogens that are excluded from the United States by law or whose entry is restricted by USDA administrative policies. Notes: Federally licensed vaccines containing live bacteria or viruses are not subject to these classifications. These vaccines are acceptable, however, to cultures of the strains used for vaccine production, or further passages of vaccinogenic origin.
20. Class I biological safety cabinet: A ventilated cabinet for personnel protection only, having an open front with inward flow of air away from the operator. The cabinet exhaust air is filtered through a high efficiency particulate air (HEPA) filter before being discharged to the outside atmosphere. This cabinet can be used for work with low- to moderate-hazard agents where no protective coverall is required.
21. Class II biological safety cabinet: An open-front cabinet for personnel and product protection with high efficiency particulate air filtered exhaust. The HEPA-filtered exhaust air is recycled and the filtered air is recirculated. This cabinet can be used for work with low- to moderate-hazard agents. It is suitable for use with explosive and flammable substances, toxic agents, or radioactive materials.
22. Class III biological safety cabinet: A gas-tight cabinet providing complete isolation for personnel and product protection with a HEPA-filtered air supply and a HEPA-filtered exhaust. The HEPA-filtered air and exhaust are conducted in the same cabinet. This cabinet provides the highest containment and may be utilized for all activities involving high-hazard agents.
23. Class IV: A population of cells derived, by axenic reproduction, from a single cell. Every cell in the population is presumed to be genetically identical. In recombinant DNA research, every cell in a clone contains the same recombinant DNA sequences.
24. Codon: The orderly array of codons which are subunits of a gene.
25. Chromosome: A linear rod-shaped body(s) in the nucleus of a cell that contains genetic information for that cell. A collection of genes.
26. Coenzyme: A molecule or a component of a molecule which is required for the enzyme to function properly.
27. Eukaryotic cell: A cell that contains a nucleus with a nuclear membrane surrounding multiple chromosomes; also contains eukaryotic organelles.
28. Gene: The smallest portion of a chromosome that contains the hereditary information for the production of a protein.
29. Genetic engineering: Directed intervention with the content and/or organization of an organism's genetic complement.
30. Genome: The complete set of hereditary information in a cell as the chromosomes in...
SUGGESTED REFERENCES FOR ADDITIONAL READING


particularly the Deputy Director for Science, information on the activities and investigation; regarding NIH responsibilities for the publication of the "Nucleic Acid Reombinant Scientific Memoranda" (NARS). Major announcements in NARS, such as distribution of guidelines, should be solicited and procedures, announcements of certified host-vector systems, training courses, workshops, conferences, etc., will be coordinated with ORDA.

III. Division of research grants, ORDA will make recommendations for Scientific Review, DRS on procedures for the review of grant applications involving recombinant DNA technology. On request, ORDA will brief executive secretaries and study sections on NIH policies and procedures.

Involvement of DRG in the processing of grant applications is discussed in Appendix A.

IV. Institutes and divisions, Institutes and Divisions will be required to report to ORDA on all activities involving recombinant DNA technology, including: Intramural research projects, extramural grants and contracts, workshops, training courses, conferences, etc. BIDs will provide ORDA with copies of all incoming and outgoing correspondence dealing with recombinant DNA research. Awarding components must consult with ORDA prior to issuing Requests for Proposals (RFPPs) for projects which may result in the processing involving recombinant DNA technology. Procedures for obtaining information on extramural research, and for review of final reports on projects proposed in this memorandum are presented in Appendix C.

ORDA will be a source of information for the Institutes and Divisions, and their initial recommendations will be processed with ORDA. ORDA may establish an inter-BID Recombinant DNA Coordinating Committee, as needed, and make recommendations on the processing of grant applications.

V. Special NIH relationships, ORDA will maintain close working relationships with the Deputy Director for Research, NIG, the Associate Director for Environmental Health and Safety, NR, and the NIH Biohazards Committee for NIH administrative, funding, and policy issues. ORDA will coordinate their activities on matters relating to recombinant DNA technology. The Office of Research Grants will be the primary responsibility for matters relating to physical containment of recombinant DNA materials, and will continue to maintain a register of the locations of these materials within the country and abroad. However, plans for site inspections of physical containment facilities currently or envisaged to be engaged in recombinant DNA research, and of other facilities as deemed necessary, will be coordinated through ORDA, and copies of site visit reports will be filed with ORDA.

VI. Federal relationships, ORDA will direct its efforts to developing relationships with other federal agencies concerned with recombinant DNA technology, including but not limited to the following: National Institutes of Health, National Science Foundation, Energy Research and Development Administration, Department of Agriculture, Environmental Protection Agency, National Aeronautics and Space Administration, and the Occupational Safety and Health Administration. ORDA should be mentioned that representatives of the National Academy of Sciences and National Science Foundation Grants and Deadlines Committee of the Recombinant Advisory Committee on a regular basis, and the National Aeronautics and Space Administration and the Energy Research and Development Administration have representatives on this committee.

VII. Non-Federal and international relationships, ORDA will maintain close relationships with private foundations, professional societies, scientific journals and industry, and to coordinate NIH policies with other federal agencies. ORDA will maintain frequent contact with the European Molecular Biology Organization.

The Deputy Director for Science, in the formation of area committees composed of members of a given institution and/or other organizations bearing responsibility for the management and health-related issues of recombinant DNA technology. ORDA will receive directly from such institutions information on the processing of grant applications. The minimum information should include the names, addresses, and members of the committee. Institutions will be notified by the appropriate instrument (NIH Guide, NIH News, etc.) of the necessity for filing this information with ORDA.

As stipulated in the Guidelines, ORDA will receive directly from such institutions information on the processing of grant applications. The minimum information should include the names, addresses, and members of the committee. Institutions will be notified by the appropriate instrument (NIH Guide, NIH News, etc.) of the necessity for filing this information with ORDA.

ORDA will review the composition of institutional biohazards committees for compliance with the recommendations stated in the Guidelines. ORDA may require the following information on a periodic basis: names and addresses of committee members; the composition of the committee; the institution represented by the committee; the procedures for reporting to the appropriate institutional authorities.

ORDA will receive from investigators information on the development of new recombinant DNA technologies and, information bearing on the Guidelines, such as technical information relating to recombinant DNA technology and new safety procedures or innovations.

ORDA will receive and file these reports and, as appropriate, bring them to the attention of other appropriate officials of NIH, the Office of Research Safety, NCI, and the Recombinant Advisory Committee or subcommittees. ORDA may, after review, recommend appropriate action to the Deputy Director for Science, NIH.

ORDA will be responsible for evaluating recombinant DNA safety practices and procedures, or equipment or facility failure. ORDA will receive from investigators information on the development of new recombinant DNA technologies and, information bearing on the Guidelines, such as technical information relating to recombinant DNA technology and new safety procedures or innovations.

ORDA will receive and file these reports and, as appropriate, bring them to the attention of other appropriate officials of NIH, the Office of Research Safety, NCI, and the Recombinant Advisory Committee or subcommittees. ORDA may, after review, recommend appropriate action to the Deputy Director for Science, NIH.

ORDA will be responsible for coordinating the activities of the Recombinant DNA Advisory Committee and all other groups involved in recombinant DNA technology, including but not limited to the following: National Institutes of Health, Office of Research Safety, NCI, and the Recombinant Advisory Committee or subcommittees. ORDA may, after review, recommend appropriate action to the Deputy Director for Science, NIH.
NOTICES

VI. Award of non-competing renewals and incrementally-funded contracts. Each non-
competing renewal of a grant or subsequent budget of an incrementally-funded contract utilizing recombinant DNA technology must be accompanied by an updated Certificate of Responsible Statement reflecting the appropriate institutional biosafety committee. Prior to any award of this type the program official in the awarding component may request a lower level of containment for reviewing the application for conformity with the Guidelines, for determining whether the proposed project or changes do not require a higher level of containment than was required in the application as reviewed and approved, or for ensuring that the required documents are properly executed. The program official will then forward ORDA a copy of the application and the certification statement, along with a request for clearance to award. The latter will include a statement to the effect that the program official has reviewed the application for conformity with the Guidelines, and that the proposed containment levels are adequate. Thereafter, the procedures described in V will be followed, and BIDs will forward ORDA a copy of all award statements involving these projects.

If the investigator proposes to significantly alter a previously approved non-competing renewal or subsequent budget period of an incrementally-funded contract, the program official may request an updated Certificate of Responsible Statement. The investigator will be required to submit an updated Certificate of Responsible Statement along with a budget proposal to ORDA prior to forwarding the request to ORDA.

VII. Changes in awarded projects. Since in many cases the NIH supports projects for project periods longer than one year, a number of situations will arise in funded projects. One situation arises when an investigator makes a decision to utilize recombinant DNA technology after the project has been reviewed and awarded. Another situation arises when an investigator decides to do DNA segments other than those originally reviewed and upon which higher levels of containment may be required. In these cases, and in all cases in which an investigator wishes to significantly alter an approved protocol, the investigator must first apply to the NIH awarding component for permission before proceeding. This requirement should be made clear both in the application for support (NIH Manual, NIH Guide, etc.) and in the subsequent acceptance of an incrementally-funded contract. The Investigator must then submit to ORDA a request for review and approval of the project changes. The request must include a full description of the proposed changes, including any new potential health and safety risks, along with a copy of the Certificate of Responsible Statement reflecting the appropriate institutional biosafety committee.

The program official in the awarding component has the responsibility for reviewing the request in light of the Guidelines, for ensuring that the required documents are properly executed, and for forwarding to ORDA a copy of all the documents along with a recommendation. The latter shall include the program official’s independent assessment of the biological containment required by the NIH Guidelines, and a recommendation as to how to proceed. ORDA will review the request and, when appropriate, refer the request to the initial review group, the Recombinant Advisory Committee, or ad hoc consultants.

* * * before containment conditions lower than the ones used to clone the DNA can be adopted, the investigator must obtain approval from the granting agency. Such ap-
proval would be contingent upon data concerning: (a) The absence of potentially harmful properties of the vector. (b) The absence of indigenous tumor viruses or which code for toxic substances. (c) The relationship between the recombinant DNA molecules and their insertion into organisms. (d) The participation of the biological properties of the vector.

This stipulation for NIH approval may be one of the most difficult sections of the Guidelines to implement. This is because of the technical nature of the data to be evaluated, and because of the volume of requests which can be anticipated. The following proposed procedures are especially viewed as a feasibility trail.

An investigator who wishes to use lower levels of containment for characterized clones derived from shotgun experiments must state, in writing, the justification for the request to the program official of the NIH awarding component. This justification will provide data on (a), (b), and (c) as stated. The program official will retain the original request in the awarding component's file, and forward a copy to ORDRA. If ORDA does not concur with the recombinant DNA Molecule Program Advisory Committee, the procedure described in this memorandum is followed. If ORDA does concur with the recombinant DNA Molecule Program Advisory Committee, the request will then be sent to the Associate Director for Environmental Health and Safety, who may appeal. The final decision rests with the Deputy Director for Science, NIH. This decision may be referred to the Recombinant Advisory Committee or to subcommittees thereof for evaluation, or, if a precedent has been established, will make a decision independently. The decision will be forwarded to the program official who may consider the decision along with the Deputy Director for Science, NIH.

IX. Large-scale experiments. The Guidelines state that:

- * • at this time large-scale experiments (e.g., more than 10 liters of culture) with recombinant DNA molecules known to make harmful products are not to be carried out • * • . However, experiments in this category may be exempted from this rule if special biological containment precautions and equipment, or large-scale operations, are used, and provided that these experiments are expressly approved by the Recombinant DNA Molecule Program Advisory Committee.

An investigator who wishes to conduct such experiments must submit a request, along with a protocol describing the research and desired containment. This protocol will be retained by the Recombinant DNA Molecule Program Advisory Committee. In the event that an investigator wishes to conduct such experiments in the future, the request will be considered. If ORDA does not concur with the Recombinant Advisory Committee or subcommittees thereof, the program official will then request the attention of the Recombinant Advisory Committee to permit continued use of these clones already in existence and constructed under Asilomar guidelines. Presumably, the use of these clones will be permitted to continue until the Recombinant Advisory Committee or a subcommittee thereof, has rendered its opinion.

The above procedures assume that all investigators are already at least in compliance with Asilomar guidelines. If projects are identified which do not comply with the Asilomar guidelines, other strategies will be brought to the immediate attention of the Deputy Director for Science, NIH and the Recombinant Advisory Committee.

APPENDIX D RECOMBINANT DNA RESEARCH Guidelines as published in the FEDERAL REGISTER, Part II, July 7, 1976

On Wednesday, June 23, 1976, the Director, National Institutes of Health, with the concurrence of the Secretary of Health, Education, and Welfare, and the Assistant Secretary for Health, Issued guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules. The NIH is also undertaking an environmental impact assessment of these guidelines for recombinant DNA research in accordance with the National Environmental Policy Act of 1969.

The NIH Guidelines establish carefully controlled conditions for the conduct of experiments involving the production of such molecules and their insertion into organisms such as bacteria. These Guidelines are the recommendations contained in the 1975 "Summary Statement of the Asilomar Conference on Recombinant DNA Molecules." The Guidelines would be subject to review under less strict conditions than the NIH Guidelines. The chronology leading to the present Guidelines is described in detail in the NIH Director's decision document that follows. In summary, scientists engaged in recombination research called, in 1974, for a moratorium on certain kinds of experiments until an international meeting could be convened to consider the potential hazards of recombinant DNA molecules. The NIH was requested to establish a committee to provide advice on recombinant DNA technology. The international meeting was held at the Asilomar Conference Center, Pacific Grove, California, in February 1975. The consensus of this meeting was that certain experiments should not be done at the present time, but that most of the work on construction of recombinant DNA molecules should proceed with appropriate physical and biological barriers. The Asilomar Conference report also
made interim assignments of the potential risks associated with different types of experiments. The NIH then assumed responsibility for translating these interim assignments into detailed guidelines for research.

The initial decision by the NIH Director on these Guidelines was reached after extensive scientific and public airing of the issues during the sixteen months that have elapsed since the Asilomar Conference. The issues were discussed at public meetings of the Recombinant DNA Molecule Program Advisory Committee (Recombinant Advisory Committee) and the Advisory Committee to the NIH Director. The Recombinant Advisory Committee extensively debated three different versions of the Guidelines during this period.

The Advisory Committee to the NIH Director, augmented with consultants representing law, ethics, consumer affairs and the environment, was asked to advise as to whether the proposed Guidelines balanced responsibilities to protect the public with the potential benefits through the pursuit of new knowledge. The many different points of view expressed at this meeting were taken into consideration in the decision.

The NIH recognizes a special obligation to disseminate information on these guidelines as widely as possible. Accordingly, the Guidelines will be sent to all of the approximately 25,000 NIH grant and contract recipients, professional societies which represent scientists working in this area will also be asked to endorse the Guidelines. The Guidelines will be sent to medical and scientific journals and editors of these journals will be asked to request that investigators include a description of the physical and biological containment procedures used in any recombinant research. International health and scientific organizations will also receive copies of the guidelines for their review.

Filing of an environmental impact statement will provide opportunity for the scientific community, State and local agencies and the general public to address the potential benefits and hazards of this research area. In order for there to be further opportunity for public comment and consideration, these guidelines are being offered for general comment in the Federal Register. It must be clearly understood by the reader that the material that follows is not proposed rulemaking in the technical sense, but is a description which will precede based on the many guidelines before the Advisory Committee to the NIH Director.

C. Implementation Beyond the Pervue of NIH

D. Environmental Policy

II. Methods of Containment (See Guidelines II)

III. Prohibited Experiments (See Guidelines III)

IV. Permissible Experiments: E. Coli K-12 Host-Vector Systems (See Guidelines IV)

V. Classification of Experiments Using the E. Coli K-12 Containment Systems (See Guidelines V)

VI. Classification of Experiments Using Containment Systems Other than E. Coli K-12 (See Guidelines VI)

VII. Roles and Responsibilities (See Guidelines IV)

INTRODUCTION

Today, with the concurrence of the Secretary of Health, Education, and Welfare and the Assistant Secretary for Health, I am releasing guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules (molecules resulting from the recombination in cell-free systems of segments of deoxyribonucleic acid, the material that determines the hereditary characteristics of organisms, and the potential hazards associated with the conduct of experiments involving the introduction of such recombinant molecules into organisms, such as bacteria. The chronology leading to the present guidelines and the decision to release them are outlined in this introduction.

In addition to developing these guidelines, the National Academy of Sciences, Committee on the Potential Biological and Ecological Hazards of the Asilomar DNA Molecule Program (hereafter "Recombinant Advisory Committee") was established to advise the Secretary, HHS, the Assistant Secretary for Health, and the NIH, concerning a program for developing procedures which will minimize the spread of such molecules within human and other populations; and (ii) developing guidelines for investigators working with potentially hazardous recombinant DNA molecules.

On October 7, 1974, the NIH Recombinant DNA Molecule Program Advisory Committee (hereafter "Recombinant Advisory Committee") was established to advise the Secretary, HHS, the Assistant Secretary for Health, and the NIH, concerning a program for developing procedures which will minimize the spread of such molecules within human and other populations, and for developing guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

The international meeting proposed in the "Science" article (185, 933, 1974) was held in February 1975 at the Asilomar Conference Center, Pacific Grove, California. It was sponsored by the National Academy of Sciences and supported by the National Institutes of Health and the National Science Foundation. One hundred and fifty people attended, including 53 foreign scientists from 15 countries, 16 representatives of the press, and 4 attorneys.

The conference reviewed progress in research on recombinant DNA molecules and discussed various containment levels or physical containment, the biological hazards of the work. Participants felt that experiments on construction of recombinant DNA molecules might involve various kinds of potential biological and physical containment, and that the conference should make recommendations for matching levels of containment with levels of possible hazard for various types of experiments. Certain experiments were judged to pose serious potential dangers that the conference recommended against their being conducted at the present time.

A report on the conference was submitted to the Assembly of Life Sciences, National Research Council, NAS, and approved by its Executive Committee on March 20, 1975. The summary statement of the report was published in "Science," 186, 981 (1975), "Nature" 253, 442 (1975), and "Proceedings of the National Academy of Sciences," 72, 1981 (1975). The report noted that "in many countries steps are already being taken by national bodies to formulate codes of practice for the conduct of experiments with known or potential biological hazard. Until these are
established, we urge individual scientists to use the proposals in this document as a guide."

The NIH Recombinant Advisory Committee held its first meeting in San Francisco immediately after the Asilomar conference. It proposed that NIH use the recommendations of the Asilomar conference as guidelines for research until the committee had an opportunity to define its guidelines, and that it prepared draft guidelines for current members of the committee, knowledgeable in the fields of recombinant DNA. These guidelines are to be discussed at the next meeting.

The NIH committee, beginning with the draft guidelines prepared by the committee, prepared proposed guidelines for research with recombinant DNA molecules at its third meeting, held on July 18-19, 1976, in Woods Hole, Massachusetts.

Following this meeting, many letters were received which were critical of the guidelines. The majority of critics felt that they were too lax, others that they were too strict.

A fourth committee meeting was held on December 4-5, 1976, in La Jolla, California. For this meeting a "variorum edition" had been prepared, comparing line-for-line the Hogness, Woods Hole, and Kutter guidelines. The committee reviewed these, voting item-by-item for the preference among the variations and, in many cases, adding new material. The result was the "Proposed Guidelines for Research Involving Recombinant DNA Molecules," which were referred to the Director, NIH, for a final decision in December 1976.

As Director of the National Institutes of Health, I called a special meeting of the Advisory Committee to the Director to review these proposed guidelines. The meeting was held at NIH, Bethesda, on February 9-10, 1976. The Advisory Committee is charged to advise the Director that:

The object of these guidelines is to ensure that experimental DNA recombinant research will have no ill effects on those engaged in the work, on the general public, or on the environment. The science of their construction is supervision of potential experiments by class, determined by the nature and level of the possible hazards of the recombinant organisms. Containment is defined as physical and biological. Physical containment involves the isolation of the research by procedures that have evolved over many years of experience in laboratories studying infectious microorganisms—"containment" at the biological containment level—is that used in most routine bacteriology laboratories. P2 and P3 afford isolation or containment from the environment. P2 and P3 afford isolation or containment from the environment. P4 contains—"the first physical barrier"—the most extreme measures used for containing virulent pathogens, and permits no escape of contaminated air, water, or untreated materials. "Biological" containment is the use of vectors or hosts that are crippled by the vector or host to the extent that the recombinants are incapable of surviving under natural conditions.

The experiments now permitted under the guidelines involve no known additional haz-

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To the workers or the environment beyond the relatively low risk known to be associated with the use of recombinant DNA. The relative hazards are speculative and therefore not quantifiable. In a real sense they are considerably less than the benefits, which are clearly derivable from the projected research. For example, the ability to produce, through "natural" recombination, relatively large amounts of pure DNA from the chromosomes of any living organism will have a profound effect in many areas of biology. No other procedure, not synthetic nor natural, provides pure material corresponding to particular genes. DNA "probes," prepared from the chromosomes of one species, may be used to provide evidence about the presence or absence, the organization, and the expression of genes in health and disease. Potential medical advances were noted by scientists active in this research area, who were present at the meeting of the Director's Advisory Committee. The importance of these developments is clear and of enormous importance, for example, the opportunity to explore the malfunctioning of cells in complicated diseases. Our ability to understand a variety of hereditary defects may be significantly enhanced, with amelioration of their effects. The potential to elucidate mechanisms in certain cancers, particularly those that might be caused by viruses.

Aside from the potential medical benefits, a whole host of other applications in science and technology have been envisioned. Examples are the large-scale production of enzymes for industrial use and the development of bacteria that can digest and destroy oil spills in the sea. Potential benefits in agriculture include the use of recombinant DNA to increase disease resistance and fix nitrogen in certain plants, permitting increased food production.

While the projected research offers the possibility of many benefits, it is important only with assurance that potential hazards can be controlled or prevented. Some commentators are concerned that nature might maintain a barrier to the exchange of DNA between prokaryotes and eukaryotes (higher organisms) in a way that could block uncontrolled or uninhibited use of this technology. They further argue that expression of the foreign DNA may alter the host in unpredictable and undesirable ways. Conceivable harm could result. If the altered host has a competitive advantage that it will foster its survival in some niche within the ecosystem. Other commentators believe that the endless experiments in recombination of DNA within nature have contributed to the beginning of life on the earth, and which have occurred in part for the evolution of species, has led to an exchange of DNA between widely disparate species. They argue that proviruses such as bacteria in the intestine of the eukaryotic host and the failure of the altered proviruses to be detected or to a sharply limited capacity of such recombinants to survive. Thus nature, this argument runs, has already tested the possibility of harmful recombination and any results are already part of the ecosystem. The fact is that we do not know which of the above-stated propositions is correct. The scientific community, exemplified by the Asilomar conference and the deliberations attendant upon preparing these guidelines, has indeed indicated a desire to proceed with research in a conservative manner. And most of the concerns prevalent during these deliberations were, while urging caution, has also favored proceeding. There are three European groups that are already working on recombinant DNA research and these are the Working Party on Experimental Manipulation of the Genetic Composition of Microorganisms, whose "Ashby Report" was presented to parliament in the United Kingdom by the Secretary of State for Education and Science in January 1975; the Advisory Committee on Medical Research of the World Health Organization, whose recommendations were published in July 1976; and the European Molecular Biology Organization Standing Committee on Recombinant DNA Research. There are no means for a flat prohibition of such research throughout the world community of science. There is no need to attempt it. It is likely that the evaluation will be conditional on the preparation and application of these guidelines. A full medical review of some of the containment practices in other work that is not technically defined as recombinant DNA research with these guidelines will lead to beneficial results. Recombinant DNA research with which these guidelines are concerned involves microorganisms such as bacteria or viruses or "cells" of higher organisms in the ecosystem. It is extremely important for the public to be aware that his research is not yet perfected to the point where strains of bacteria, animals, or plants may occur. The guidelines will be published in the Federal Register forthwith to allow for further public comment.

A. IMPLEMENTATION CONSIDERATIONS WITHIN THE PURVIEW OF NIH

All the commentators had suggestions concerning the structure and function of decision making as it relates to the principal investigator, the local biosafety committee, the peer review group, and the NIH Recombinant Advisory Committee. These comments mainly concerned the formulation of the guidelines relating to roles and responsibilities of investigators, their institutions, and the National Institutes of Health are presented below.

Of considerable concern to all commentators was the process by which NIH would implement the guidelines. The scientific community generally urged that there be no Federal regulations, while some comments recommended that the regulatory process be initiated by the NIH. Many who opposed changing the proposed guidelines felt that Federal regulations expressed concern for flexibility and administrative efficiency, which could best be achieved, in their view, through voluntary compliance. Other commentators, however, believed it imperative to proceed toward regulation. In their view, the guidelines could be implemented for purposes of NIH funding and would govern the conduct of experiments until regulations were in effect. Another commentator thought regulation would be harmful rather than helpful suggested that if there were to be regulations, they should be along lines similar to those that govern the sale, distribution, use, and disposal of radioisotopes.

The question of how best to proceed now that the guidelines have been released deserves careful attention. I share the concern of those who feel that the guidelines must remain flexible. It seems important that there be opportunity to change them quickly, based on new information regarding the scientific evidence, relative costs, or safety aspects of the research program.

The suggestions for regulation need further consideration at this time. While NIH has the authority to regulate not only involves the Director of NIH, but also the Assistant Secretary for Health and the Secretary of Health, Education, and Welfare. These guidelines are being promulgated now in order to afford additional protection to all concerned. Consideration of revision to the guidelines can proceed with continuing review of their content and present and future implications. Meanwhile, the NIH will continue to provide the opportunity for public comment and participation at least equivalent to that provided if steps towards regulations were to proceed immediately. The guidelines will be published in the Federal Register forthwith to allow for further public comment.

B. IMPLEMENTATION CONSIDERATIONS BEYOND THE PURVIEW OF NIH

Special concern has been expressed by many commentators regarding the application of these guidelines to the work of NIH by investigators other than its principal investigators. It has been urged that the guidelines be made applicable to recombinant DNA research conducted by other agencies in HEW and by NSF, ERDA, DoD, and other governmental departments.

Many feel that experiments conducted in colleges, universities and even in high schools require some form of monitoring. And finally, all agree that in view of the potential hazards of recombinant DNA research to the biosphere, some form of international understanding on guidelines for recombinant DNA is essential.

The committee, in the proposed guidelines, has suggested one means of achieving this description of the physical and biological containment procedures practiced in a research project be included in the publication of research results. In the scientific community this can be a powerful force for conformity. The committee feels that it is urgent to publish the guidelines, and to proceed with the recommendation to all appropriate journals. We are also prepared to take steps to disseminate the guidelines widely, and to arrange for a continuing flow of information outward concerning the activities of the Recombinant DNA Advisory Committee.
combinant Advisory Committee and the Ad
dvisory Committee to the Director, NIH, in
the evolution of the guidelines and their im-
l实施。 In response to these suggestions, I
have already held a meeting with relevant HEW
agencies and with representatives from other
departments of the Federal Government. The
purpose of the meeting was to exchange in-
formation on recombinant DNA research and
to discuss future directions. It has been an
important beginning to address a com-
mon concern of these public institutions. A
number of issues identified at the meeting
have not been well addressed by the various
departments. I believe we should adopt the
guidelines for research conducted both
in-house and supported outside. Following up,
I have begun preliminary discussions with
the Assistant Secretary for Health and
the NIH Steering Committee, to determine possible
methods to ensure adoption of the guidelines
by all Federal agencies. Encouraged by these
efforts, we held a meeting on June 2 with
representatives of industry to provide them
with full information about the guidelines and
to help determine the present and future
interests of industrial organizations in this
type of research. The meeting provided one of
the first opportunities for industry rep-
resentatives to discuss the potential opportuni-
ties and constraints of recombinant DNA
research. It is my hope that the guidelines will
be voluntarily adopted and honored by all who
support or conduct such research through-
out the United States. I believe that at least very
similar guidelines will obtain throughout the
rest of the world. NIH places the highest
priority on efforts to inform and to work with
international organizations, such as the
World Health Organization and the Inter-
national Council of Scientific Unions, with a
view to achieving a consensus on safety
standards in this most important research
area.

There has been considerable international
cooperation and activity in the past, and I
expect it to continue in the future. The
aforementioned Ashby Report, presented to
Parliament in January 1976, describes the
advances in knowledge and possible benef-
to experiments on recombinant DNA and recombi-
nant DNA molecules, and attempts to
assess the hazards in these techniques. The
Ashby meeting also had a number of inter-
national aspects, as mentioned previously. The
European Molecular Biology Organization (EMBO)
has been involved in considering recombinant DNA
research. They have closely followed the ac-
tivities of NIH, and will thus be encouraged,
believing that their research with aug-
mented cooperation and coordination. For
example, EMBO recently announced plans
for a voluntary registry of recombinant DNA
research in Europe. Following this EMBO
initiative, NIH shall similarly maintain a
voluntary registry to ensure that our in-
stitutions engaged in such research in the
United States. Plans for establishing this reg-
istry are under way.

B. ENVIRONMENTAL POLICY CONSIDERATIONS
A number of commentators urged NIH to
consider preparing an environmental im-
 pact statement on recombinant DNA re-
search activity. They evoked the possibility
that recombinant DNA molecules might escape and affect the en-
vironment in potentially harmful ways. I
am in full agreement that the potentially
hazardous effects of this research on the en-
vironment should be assessed. As discussed
throughout this paper, the guidelines are
promised on physical and biological contain-
ment to prevent the release or propagation
of recombinant DNA molecules outside the laboratory. Deliberate selective control of the en-
vironment is prohibited. In my view, the
stipulated physical and biological contain-
ment standards will help to ensure a high level
with a high degree of safety and precaution.
But I recognize the legitimate concern of
potential environmental impact to be assessed.
In view of this concern and ensuing public debate, I have reviewed the
Environmental Impact Assessment and have directed that one be undertaken.

The purpose of this assessment will be to review the environmental effects of any
research that may be conducted under the guidelines. The assessment will provide fur-
ther opportunities for others to address the potential benefits and hazards of this
most important research activity. I expect a draft of the environmental impact statement
should be completed by September 1 for
comment by the scientific community, Fed-
eral and State agencies, and the general
public.

It should be noted that the development of
the guidelines was in large part fundamenta-
to containing recombinant DNA re-
search. For example, the objectives of re-
combinant DNA research, and alternate ap-
proaches to containing recombinant DNA
have been considered. The potential hazards and risks have been analyzed. Alternative approaches to containment need to maxi-


-ize safety and minimize potential risk. And an elaborate review structure has been cre-
ated to achieve these results. From the viewpoint, however, the environ-
mental impact assessment will be yet another review that will provide further op-
portunities for public comment and public
discussion. The following comments
are a part of this discussion.

II. METHODS OF CONTAINMENT
Comments on the containment provisions of the proposed guidelines were directed to the definition of physical containment and containment
and to the safety and effectiveness of the prescribed levels. Several com-
mentators found the definition of physical con-
tainment imprecise and too subject to the
consideration for human error. Others ques-
tioned the concept of biological containment
in terms of its safety and purported effective-
ness in averting potential hazards. The com-
mentators were divided on which method of
containment would provide the safest and least
effective system to avoid hazards. Several sug-
gested that each of these methods be
incorporated, with editorial revisions, in the
final version of the guideline.

W. Emmett Barkley, Ph.D., Director of the
Office of Research Safety, National Cancer
Institute, commented on physical containment in
light of these comments. Dr. Barkley convened a special com-
mittee of safety and health experts, who met to
take full consideration of this section of the
guidelines but also the section of the rules and
responsibilities of recombinant DNA and
their institutions. The committee thoroughly
reviewed the section on physical containment and recombinant DNA
number of changes. The Recombinant DNA Advisory
Committee, meeting on April 1-2, 1976, reviewed the recommenda-
tions of the Barkley group. These were incor-
porated, with editorial revisions, in the final
version of the guidelines.

The present section on physical contain-
ment is directly relevant to these com-
mentators who asked for greater detail and
clarification. Although different in detail, the
new level standards approximate those
given by the Center for Disease Control for
human etiologic agents and by the National
Cancer Institute for onco-viruses. For
each of the physical containment elements
have been excluded, and only those items

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The continued use of E. coli as a host has drawn considerable comment, including some suggestions that its use be prohibited presently or within a specified time limit. It should be stressed that the use of E. coli as detailed in the guidelines is limited to E. coli K-12, a strain that has been carried in the laboratory for decades, and does not involve the use of any strain of E. coli that is freshly isolated from a natural source. E. coli K-12 is a specific strain, and one that is easily isolated and grown in the laboratory. Since E. coli acquires resistance naturally, the prohibition directed against increasing resistance has not always been effective. The statements that have been deleted concern the use of E. coli for research that involves the deliberate release of the organism into the environment. The continued use of E. coli for this purpose is prohibited by the guidelines.

Remarks that would extend the range of resistance of this bacterium to therapeutically useful drugs and disinfectants, and thus seem to be in conflict with the general prohibition on research that involves the deliberate release of the organism into the environment, have been deleted. The use of E. coli for research that involves the deliberate release of the organism into the environment is prohibited by the guidelines.

VI. CLASSIFICATION OF EXPERIMENTS USING THE E. COLI K-12 HOST-VECTORS SYSTEM

The guidelines assign different levels of containment for experiments in which DNA from different sources is to be introduced into an E. coli K-12 host-vector system. The variation is based on both facts and assumptions. There are some prokaryotic bacteria which constantly exchange DNA with E. coli. Here it is assumed that experimental conditions beyond those obtained in careful, routine microbiology laboratories are superfluous, because any exchange experiments have undoubtedly been performed already in nature.

In every instance of artificial recombination, considerations must be given to the possibility that foreign DNA may be translated into protein (expressed), and also to the possibility that normally expressed genes of the host may be repressed and thus change, undesirably, the characteristics of the cell.

It is essential that the system be one that is completely defined and that provides in the near future a useful system that is J. coli E-2, a strain that has been carried in the laboratory for decades, and does not involve the use of any strain of E. coli that is freshly isolated from a natural source. E. coli K-12 is a specific strain, and one that is easily isolated and grown in the laboratory. Since E. coli acquires resistance naturally, the prohibition directed against increasing resistance has not always been effective. The statements that have been deleted concern the use of E. coli for research that involves the deliberate release of the organism into the environment. The continued use of E. coli for this purpose is prohibited by the guidelines. The guidelines assign different levels of containment for experiments in which DNA from different sources is to be introduced into an E. coli K-12 host-vector system. The variation is based on both facts and assumptions. There are some prokaryotic bacteria which constantly exchange DNA with E. coli. Here it is assumed that experimental conditions beyond those obtained in careful, routine microbiology laboratories are superfluous, because any exchange experiments have undoubtedly been performed already in nature.

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Recombination experiments will create new genetic combinations. When prokaryotic DNA is transferred into eukaryotic cells, the new combination of genes typically resembles the parent prokaryotic DNA more closely than it does the eukaryotic DNA from which it has been transferred. Therefore, prokaryotic DNA is more dangerous than eukaryotic DNA. However, this does not mean that all prokaryotic DNA is dangerous. Some prokaryotic DNA is relatively benign and can be used safely. The key is to identify the type of prokaryotic DNA that is being used and to determine whether it poses a significant risk to human health.

There are two main types of recombinant DNA experiments: in vivo and in vitro. In vivo experiments involve introducing DNA into living cells, while in vitro experiments involve using cells in a laboratory setting. In vivo experiments are more dangerous because they involve introducing DNA into living organisms. In vitro experiments are generally considered safer because the DNA is not introduced into living organisms.

The guidelines for recombinant DNA experiments are designed to protect human health and the environment. The guidelines require that experiments be reviewed by a panel of experts before they are approved. The panel of experts will evaluate the potential risks and benefits of each experiment and will make recommendations about whether the experiment should be approved.

The guidelines also require that experiments be performed under controlled conditions. This will help to minimize the risk of accidental releases of recombinant DNA into the environment. In addition, the guidelines require that experiments be monitored to ensure that they are being performed safely.

In conclusion, the guidelines for recombinant DNA experiments are designed to protect human health and the environment. These guidelines are based on the best available scientific data and are regularly updated to reflect new information. The guidelines are designed to be flexible and to allow for the safe and responsible use of recombinant DNA.

References:
1. The Recombinant DNA Advisory Committee.
2. The National Institutes of Health.
3. The American Association for the Advancement of Science.
4. The World Health Organization.
5. The European Union.

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was urged that containment levels for this, class of experiment be increased. On the basis of our consultations and conditions appropriate to the potential hazards involved, they are more stringent than conditions obtaining in many laboratories where such viruses are used as non-DNA recombinant experiments.

VI. CLASSIFICATION OF EXPERIMENTS USING CONTAINMENT SYSTEMS OTHER THAN E. COLI K-12

1. No issue with regard to these guidelines raised more comment than the use of animal viruses as vectors. Of special concern to many commentators was the use of the simian (monkey) virus 40 (hereafter “SV40”). Some suggested a complete ban on the use of this virus; others urged its retention under the most careful conditions, but developed for its use in the guidelines. It is clear that much of the success of the guidelines will lie in the wisdom with which hazards committee to serve as a source of advice, decisions regarding the use of SV40 would require us with sufficient sophistication to ensure its safe handling under the conditions for this class of experiments and review this section of the guidelines. The group met to address these concerns, a group of extensive knowledge we have of SV40 virus production situations in which the DNA from plants will be introduced into research. Work with SV40 virus will be done at containment levels from EK3 to EK4 for experiments in which the DNA from plants is used in conjunction with the E. coli K-12 cloning vector system, thereby setting containment in this instance at the same level required for experiments with lower-eukaryote DNA.

VII. ROLES AND RESPONSIBILITIES

1. Most commentators had suggestions for the section on the roles and responsibilities of investigators, their local institutions, and NIH. Commentators generally urged openness, careful evaluation of risk, and in the process, emphasizing shared responsibility and accountability from the local to the national level. The committee, with the benefit of several years of experience with guidelines in light of these comments and have asked the Recombinant Advisory Committee to prepare a draft by the end of this year.

It is clear that much of the success of the guidelines will lie in the wisdom with which they are implemented. Because of the importance of public confidence in terms of safety programs and plans, we have carefully weighed the comments and suggestions made in this regard. NIH has a special responsibility to take a leading role in ensuring that safety programs are part of all recombinant DNA research. Dr. Batselier and a special convened committee were asked to provide greater detail for safety, accident, and training plans for this section of the guidelines. Based on these recommendations, the section has been extensively rewritten to clarify the respective responsibilities of the principal investigator, the institutional biosafety committee, the NIH initial review group (study section), the NIH Recombinant DNA Molecule Program Advisory Committee, and NIH.

This section has a definitive administrative framework for ensuring that safety is an essential and integrated component of research involving recombinant DNA molecules. The guidelines require investigators to institute, monitor, and evaluate containment and safety practices and procedures. Before results are obtained, the investigator must have safety and accident plans in place and training exercises for the staff well under way.

Some commentators suggested that the institutional biosafety committee be strengthened. There is evidence that polyoma virus as the vector be strengthened. There is evidence that polyoma virus may be more effectively disinfected by Clorox and autoclaving. These are customary procedures for disinfecting glassware and other items used in SV40 animal-cell work. Some commentators suggested that the guidelines include the containment requirements for polyoma virus as the vector be strengthened. There is evidence that polyoma virus is more fully covered in an appendix to these guidelines.

1. One member disented from this position. During the discussion, additional language was recommended (and adopted) to ensure that polyoma virus as the vector be strengthened. This system, with its inserted non-SV40 DNA segment, does not replicate in human cells with significantly more efficacy than does SV40.

2. Several commentators found the guidelines inadequate regarding experiments with the simian (monkey) virus 40 (hereafter “SV40”). Some suggested a complete ban on the use of this virus; others urged its retention under the most careful conditions, but developed for its use in the guidelines. It is clear that much of the success of the guidelines will lie in the wisdom with which they are implemented. Because of the importance of public confidence in terms of safety programs and plans, we have carefully weighed the comments and suggestions made in this regard. NIH has a special responsibility to take a leading role in ensuring that safety programs are part of all recombinant DNA research. Dr. Batselier and a special convened committee were asked to provide greater detail for safety, accident, and training plans for this section of the guidelines. Based on these recommendations, the section has been extensively rewritten to clarify the respective responsibilities of the principal investigator, the institutional biosafety committee, the NIH initial review group (study section), the NIH Recombinant DNA Molecule Program Advisory Committee, and NIH.

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Act (OSHA). This is an area of importance to the local institutions under Federal and State law, but need not be included as a requirement of the contract for research. It is essential to maintain liaison with the Occupational Safety and Health Administration (Department of Labor) to ensure maximum Federal cooperation in this venture.

I would also encourage all institutions, as suggested by the Advisory Committee, to consider the insurance implications of their usage of recombinant DNA and to include the necessary precautions in insurance policies when available. In this regard, it is important to note that there has been no report of injury to personnel, but the potential exists for accidental exposure to potentially hazardous recombinant DNA. This and other matters will be reviewed by the Recombinant DNA Advisory Committee at its next meeting.

3. The comments also include a request that the Recombinant DNA Advisory Committee be allowed to review experimental procedures in order to enhance the safety of recombinant DNA work. This recommendation will be considered by the Advisory Committee.

4. Several comments have been made concerning the structure, function, and scope of the Recombinant DNA Advisory Committee. The comments reflect a desire for a more active role for the Advisory Committee and for a greater degree of public involvement in the review of recombinant DNA projects.

5. The final day of the meeting focused on the future of the Recombinant DNA Advisory Committee. The committee discussed the need for continued funding, the importance of public participation, and the need for ongoing evaluation of the success of the advisory committees. The committee also discussed the need for additional training for personnel involved in recombinant DNA research.

6. The advisory committee is committed to ensuring the safety of recombinant DNA research. The comments suggest that the committee continue its efforts to develop guidelines and procedures to ensure the safety of recombinant DNA research.

7. In conclusion, the comments suggest that the Recombinant DNA Advisory Committee continue its efforts to develop guidelines and procedures to ensure the safety of recombinant DNA research. The committee is committed to ensuring the safety of recombinant DNA research and will continue to work towards this goal.

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A. Standard practices and training.
B. Physical containment levels.
1. P1 Level (Minimal).
2. P2 Level (Low).
3. P3 Level (Moderate).
4. P4 Level (High).

C. Shipment.

D. Biological containment levels.

III. Summary of Workshop on the Design and Construction of Recombinant DNA Molecules.

IV. Roles and Responsibilities.

A. Investigator.
B. Institution.
C. NIH Initial Review Group (Study Section).

D. NIH Recombinant DNA Molecule Program Advisory Committee.

E. NIH Staff.

V. Footnotes.

VI. References.

VII. Members of the Recombinant DNA Molecule Program Advisory Committee.

APPENDICES

A. Statement on the use of Bacillus subtilis in recombinant DNA technology.

B. Polyoma and SV40 Virus.


D. Supplementary Information on Physical Containment (Including Detailed Containment Levels).
known absolutely in the absence of firm experimental data-and, unfortunately, the known absolutely in the absence of firm knowledge of the potential biohazards and of the means to prevent their occurrence. Our problem then has been to construct guidelines for the dissemination of the recombinant DNA molecules requiring physical containment at the P2 level is a laboratory that possesses no special engineering design features. It is a laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P3 level. The P3 laboratory is commonly used for experiments requiring containment of hazardous agents (vii) Facilities to wash hands should be provided. (viii) The use of laboratory gowns, coats, or uniforms is discretionary with the laboratory supervisor.

P2 Level (Low). A laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P2 level is similar in construction and design to the P1 laboratory. The P2 laboratory must have access to an autoclave within the building. It may have a Biological Safety Cabinet. Work which does not produce a considerable aerosol is conducted on the open bench. Although the laboratory is not separated from the rest of the building, access to the laboratory is limited when experiments requiring special containment are being conducted. Experiments of lesser biohazard potential can be carried out concurrently in the less heavily occupied areas of the same laboratory.

The P2 laboratory is commonly used for experiments involving recombinant DNA molecules requiring physical containment at the P2 level. It is a laboratory that requires no special engineering design features. It is a laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P1 level. The P1 laboratory is generally conducted on open benches. Special containment features are not required.

P1 Level (Minimal). A laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P1 level is a laboratory that possesses no special engineering design features. It is a laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P1 level. The P1 laboratory is generally conducted on open benches. Special containment features are not required.
The following practices shall apply to all experiments involving recombinant DNA physical containment: (i) Laboratory doors shall be kept closed while experiments are in progress. (ii) Only personnel physically present in the laboratory at the time of the potential bioshazard shall enter the laboratory. (iii) Children under 12 years of age shall not enter the laboratory. (iv) Surfaces shall be decontaminated daily and immediately following spills of recombinant DNA materials. (v) Liquid wastes of recombinant DNA materials shall be decontaminated before disposal. (vi) Solid wastes contaminated with recombinant DNA materials shall be decontaminated before disposal. (vii) Biological Safety Cabinets 1 and other physical containment equipment shall be used for all procedures that produce aerosols of recombinant DNA materials (e.g., pipetting, plating, transfer operations, grinding, blending, drying, sonication, shaking, etc.). (viii) Biological Safety Cabinets 1 and other equipment shall be decontaminated following the completion of the experiments and area cleaned with them. (ix) Liquid wastes containing recombinant DNA materials shall be decontaminated or packaged in a durable leak-proof container before removal from the laboratory. Packaged material shall be sterilized before disposal. Contaminated materials that are to be processed and reused must be sterilized in the controlled laboratory area or placed in a durable leak-proof container before removal from the laboratory. This container shall be sterilized before the materials are processed. (x) Pipetting by mouth is prohibited; mechanical pipetting devices shall be used. (xi) Eating, drinking, smoking, and storage of food are not permitted in the working area. (xii) Facilities to wash hands shall be available within the laboratory. Persons handling recombinant DNA materials should be encouraged to wash their hands frequently and when leaving the laboratory. Insect and rodent control program shall be provided. (xiii) The use of laboratory gowns, coats, or uniforms is required. Such clothing shall be sterilized before disposal. (xiv) Biological Safety Cabinets 1 and other physical containment equipment shall be used to minimize the hazard of aerosolization of recombinant DNA materials from operations or devices that produce a considerable aerosol (e.g., blender, lyophilizer, sonicator, shaking machine, etc.). Use of this equipment shall be avoided when alternate methods are available. (xv) Biological Safety Cabinets 1 are available within the controlled laboratory area. Persons shall wash hands after experiments involving recombinant DNA materials and change gowns if contaminated. An insect and rodent control program shall be provided. (xvi) Refuge clothing is recommended. Laboratory clothing shall not be worn outside the laboratory and shall be decontaminated before it is sent to the laundry. (xvii) Raincoats, overcoats, topcoats, coats, hats, and such outerwear is required on all facility access doors and interior doors to Individual laboratory areas. Persons shall be instructed as to the appropriate safeguards to ensure their safety before entry. Such persons shall comply with the instructions and all other posted entry and exit procedures. Under no condition shall children under 15 years of age be allowed entry. (xix) All personnel shall be kept out of the laboratory only through the clothing change and shower rooms where experiments are conducted. Only persons whose entry into the facility is required on the basis of program or support needs shall be authorized to enter. Such persons shall be advised of the potential hazards and instructed to the appropriate safeguards to ensure their safety before entry. (xx) Biological Safety Cabinets 1 are available within the controlled laboratory area. The ventilation system is balanced to provide for an inflow of supply air from the access corridor into the laboratory. The general exhaust air from the access corridor shall be discharged outdoors and so dispersed to the atmosphere as to prevent undue indoor air changes. No return system of the exhaust air shall be permitted without appropriate treatment. (xxi) No work materials or vessels containing hosts or vectors containing recombinant DNA molecules requiring F3 physical containment is conducted on the bench. All such procedures are confined to Biological Safety Cabinets 1. The following practices shall apply to all experiments involving recombinant DNA physical containment: (i) The universal bioshazard sign is required on all laboratory access doors. Only persons whose entry into the laboratory is required on the basis of program or support needs shall be authorized to enter. Such persons shall be advised of the potential bioshazards before entry and they shall comply with the instructions and all other posted entry and exit procedures. Access to the facility is under strict control. A specific facility operations manual is available within the laboratory. Biological Safety Cabinets 1 are available within the facility. A F4 facility has engineering features which are designed to prevent the escape of highly lethal, severe, or dangerous recombinant DNA material. A F4 facility is either a separate building or it is a controlled area, within a building, which is completely separate from all other areas. Access to the facility is under strict control. A specific facility operations manual is available within the facility. Biological Safety Cabinets 1 are available within the facility. FEDERAL REGISTER, VOL 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
entire system has been decontaminated. (vii) No materials shall be removed from the facility unless they have been sterilized or decontaminated in a manner to prevent the release of viable pathogens to the environment. All wastes and other materials and equipment not damaged by high temperature or sterilization shall be discarded in the facility steam autoclave. Biological materials to be removed from the facility shall be transferred to a hazardous waste container. All personnel shall then be removed from the facility through a chemical decontamination tank or a chamber designed to decontaminate clothing and skin. Other materials which may be damaged by temperature or steam shall be sterilized by gaseous or vapor methods in an air lock or chamber designed for this purpose. (viii) Eating, drinking, smoking, and storage of food are not permitted in the facility. Foot-operated water fountains located in the facility corridors are permitted. Separate potable water piping shall be provided for these water fountains. (ix) Facilities to wash hands shall be available within the facility. Persons shall wash hands after experiments. (x) An insect and rodent control program shall be conducted following the completion of the experiments. (xi) Animals and plants not related to the experiment shall not be permitted in the facility. (xii) If a central vacuum system is provided, the facility shall be protected by a filter and liquid trap in addition to the branch line HEPA filter mentioned above. (xiii) Ecol K-12 samples and syringes shall be avoided when alternate methods are available. (xiv) If experiments of lesser biohazard potential are conducted in the facility concurrently with experiments requiring P4 level containment, they shall not use Biological Safety Cabinets 1 or isolated by other physical containment equipment. Work surfaces of Biological Safety Cabinets 1 and 2 shall be decontaminated following the completion of the experimental activity contained within them. Mechanical pipetting devices shall be avoided. All other practices listed above with the exception of (vi) shall apply.

C. Shipment. To protect product, personnel, and the environment, all recombinant DNA material shall be shipped in containers that meet the requirements issued by the U.S. Public Health Service, (Section 72.23 of Part 72, Title 42, Code of Federal Regulations), Department of Transportation, (Section 171.30 of Title 49, Code of Federal Regulations) and the Civil Aeronautics Board (C.A.B., No. 83, Official Air Transportation Regulations), for shipment of etiologic agents. Labeling requirements specified in these Federal regulations shall be adhered to also for the recombinant DNA materials in which any portion of the material is derived from an etiologic agent listed in paragraph (c) of 42 CFR 72.23. Additional information on packaging and shipping is given in a supplement to the guidelines (Appendix D, part 2).

D. Biological containment levels. Biological barriers are specific to each host-vector system. Hence the criteria for this mechanism of containment can be applied to the same extent as for physical containment. This is particularly true at the present time when our experience with existing host-vector systems is limited. Conclusive knowledge about projected systems are sparse. The classification of experiments with recombinant DNA is necessary for the construction of the experimental guidelines (Section III) can be accomplished with least confusion if we use the host-vector system as the primary element and the source of the insert DNA as the secondary element in the classification. We therefore can specify the nature of the biological containment under host-vector headings such as those given below for Escherichia coli K-12.

III. EXPERIMENTAL GUIDELINES

A general rule that, though obvious, deserves statement is that the level of containment required for any experiment on DNA recombinants shall never be less than that which can be justified on the basis of necessary host-vector combinations used to construct and clone the recombinant DNA (i.e., vector, host, and inserted DNA). In most cases the level of containment will be greater, particularly when the recombinant DNA is formed from species that ordinarily do not exchange genetic material. Handling the purified DNA will generally require less stringent precautions than will propagating the DNA. However, the DNA itself should be handled as though it were a potentially dangerous substance, such as one that would handle the most dangerous of the DNAs used to make it.

The above rule is self-evidently precluded certain experiments—namely, those in which one of the components is in Class 6 of the "Classification of Etiologic Agents on the Basis of Hazard" (5), as these are excluded from the United States by law and FDA administrative policy. There are additional experiments which may engender such serious biohazards that they are not to be performed at this time. These are considered prior to presentation of the containment guidelines for permissible experiments.

A. Experiments that are not to be performed. We recognize that it can be argued that certain of the recombinants placed in this category could be adequately contained at this time. Nonetheless, our estimates of the possible dangers that may ensue if that level of containment fails to be maintained that we consider it the wisest policy to at least defer experiments on these recombinant DNAs until there is more information to accurately assess that danger and to allow the construction of more effective biological barriers. In this respect, these guidelines are more stringent than those initially recommended (1).

The following experiments are not to be initiated at the present time: (i) Cloning of recombinant DNAs derived from the pathogenic organisms in Classes 3, 4, and 5 of "Classification of Etiologic Agents on the Basis of Hazard" (5), or oncogenic viruses classified by NIH as moderate risk (6), or cells known to be infected with such agents, regardless of the host-vector system used. (ii) Deliberate formation of recombinant DNAs containing genes for pyrimidine or purine cinct toxins (botoxum or diptheria toxins; venoms from insects, snakes, etc.). (iii) Deliberate creation from plant pathogenic that are likely to be transferred to man and increase virulence and host range. (iv) Deliberate release into the environment of any recombinant DNA expressing an infectious DNA molecule. (v) Transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture.

In addition, at this time large-scale experiments (e.g., more than 10 liters of culture) with recombinant DNAs known to carry harmful products or proteins are not carried out. We differentiate between small- and large-scale experiments with such DNAs because the known containment barriers normally increases with increasing scale. However, specific experiments in this category (10-100 liters) and special experimental conditions and operations are used, and provided that these experiments are expressly approved by the Recombinant DNA Molecule Program Advisory Committee.

B. Containment guidelines for permissible experiments. It is anticipated that most recombiant DNA experiments initiated before these guidelines are next reviewed (i.e., within the year) will employ E. coli K-12 host-vector systems. There are also the systems for which experimental containment guidelines may have been established, and knowledge regarding the effectiveness of the containment provided by existing hosts and vectors, and the development of more effective biological barriers.

For these reasons, E. coli K-12 appears to be the category that is well established. We have carefully considered arguments that many of the possible dangers are contained in an organism as intimately connected with man as E. coli K-12, while proceeding cautiously with E. coli, serious efforts should be made toward developing alternate host-vector systems: this subject is discussed in considerable detail in Appendix A.

We therefore consider DNA recombinants in E. coli K-12 before proceeding to other host-vector systems.

1. Biological containment criteria using E. coli K-12 host-vectors. These are host-vector systems that can be estimated to already provide a moderate level of containment, and include most of the presently available systems. The host is always E. coli K-12, and the vectors include nonconjugative plasmids (e.g., pBR322 or derivatives thereof (19-20)) and variants of bacteriophage φ (27-29).

The nonconjugative plasmid system is taken as an example to illustrate the approximate level of containment referred to in this section. The experiments involving the feeding of bacteria to humans and calves (30-32) indicate that E. coli K-12 did not usually colonize the normal bowel, and exhibited little, if any, multiplication while passing through the alimentary tract even after feeding high doses (i.e., 10^10) of bacteria per kg. However, general extrapolation of these results may not be warranted because the implantation of bacteria into the intestinal tract depends on a number of parameters, such as the nature of the intestinal flora present in a given individual and the physiological state of the inqomuc. Moreover, since viable E. coli K-12 can be found in the feces after humans are fed 10^10 bacteria in broth (30) or 2x10^9 bacteria protected by suspension in milk (31), transductional and conjugal transfer of the plasmid vectors from E. coli K-12 to resident intestinal bacteria is possible and after excretion must also be considered.

The nonconjugative plasmid vectors cannot replicate in either of the two categories of bacteria in which the presence of a conjugative plasmid for mobilization and transfer to other bacteria. The plasmidic mobilization in the nonconjugative plasmids such as F or R1dR19, the nonconjugative CoEI, CoEI1D and CoEI1C plasmids are transferred to suitable recipient strains under ideal laboratory conditions at frequencies of about 0.5, 10^4 to 10^5, and 10^6 per donor cell, respectively. These frequencies are reduced by another factor of 10^6 to 10^7 if the conjugative plasmid employed is repressed with respect to expression of donor fertility.

The experimental transfer system which most closely resembles nonconjugative plasmid transfer in nature is a triparental matting. We have carefully considered arguments that many of the possible dangers are contained in an organism as intimately connected with man as E. coli K-12, while proceeding cautiously with E. coli, serious efforts should be made toward developing alternate host-vector systems: this subject is discussed in considerable detail in Appendix A.

We therefore consider DNA recombinants in E. coli K-12 before proceeding to other host-vector systems.

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The frequency of subsequent encounters with nonconjugative plasmids is mobilized and transferred by a sequence of events in vivo that is different from that occurring in vitro. However, the frequency of transfer observed on an antibiotic-supplemented diet, it has been estimated that such tripartite nonconjugative plasmid transfer may occur at frequencies of no more than 10^{-5} to 10^{-3} per 24 hours per cell (32). In terms of sidestream cloning of plasmid DNA, it is not as accurate as those for physical containment, and are sufficient to reduce the plasmid to cause it to be dependent on a specific host, to make its replication a non-orderly procedure, and to killability such that all cells (other than the host) into which it might be transmuted with plasmids.

The occurrence of the E. coli K-12 plasmid vector should not permit survival of a transformed host vector system because it is a measurable entity. Usually, vectors and hosts, individually or in combination with a deoB(drm) mutation are at least as accurate as those for the plasmid vector carrying an easily detectable marker within an inserted DNA fragment with a cloned plasmid-host system or reduce mobilization of the Apr pimely prophage. Although 

plasmid-propagated plasmids to enter the plasmid-host complex and should reduce conditions for the selective cloning of non-plasmid DNA to other strains, and plasmids that confer resistance to known transducing phage vectors. Mutations can also be introduced into the plasmid to cause it to be dependent on a specific host, to make its replication a non-permissive condition for plasmid transfer. Other nonconjugative plasmids may also be introduced into the host (or its resident lambda prophage) with properties similar to those of the natural environment.

In terms of potential EK2 plasmid-host systems, the following types of genetic modifications should reduce survival of cloned DNA fragments. The presence of the Apr prophage in any of the three 

strains followed as a function of time. Survival of the vector and/or a cloned marker on a recombinant plasmid is not a common route of escape of plasmid DNA fragments under conditions that are possible in nature and that are also most dangerous to its propagation. For example, one might consider a tripartamental mating with a primary donor possessing a Redemption F- vector with all the necessary functions. This vector with all the necessary functions. This vector with all the necessary functions.

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the Ph-Q region, including mutations such as tr-3, cro(TS), etT, rN, O(TS), F(TS), and nin. Moreover, chloroform treatment used routinely followed by the large number of surviving cells, including possible lysogenic or plasmid carries, by more than 10^6. The deletion of the host (phage) site and inclusion of one or more of the mutations described above for phage propagation could reduce the chance of formation and survival of any lysogenic or plasmid carrier cell.

Laboratory tests should be performed with the bacterial host to measure all possible conditions should be verified periodically to attain the desired efficiencies of frequent escape of prophage vectors harbored in r^m-Su^ant strains.

When any investigator has obtained data on the level of containment provided by a particular vector, the tests should be reported as rapidly as possible to generalize awareness and evaluation of the safety features of these new vectors. Researchers should also be encouraged to make such new safer cloning systems generally available to other scientists. NILI will take appropriate steps to aid in the distribution of these safer vectors and hosts.

E. coli host-vectors. These are E. coli systems for which the specified containment shown by laboratory tests has been independently confirmed by appropriate tests in animals, including as or primates, and in other relevant environments in order to provide additional data to validate the levels of containment afforded by the EK2 host-vector systems. Evaluation of the effects of individual or combinations of mutations contributing to a higher level of containment should be performed as a means to confirm the degree of safety provided and to further advance containment by reducing even safer vectors and hosts. For the time being, no host-vector system will be considered to be a benefit to a vector system, until it is certified by the National Microbiological DNA Molecule Program Advisory Committee.

2. Classification of containment conditions of different kinds of recombinant DNAs, the status of containment is considered to be minimum. Higher levels of biological containment (EK-1>EK-2>EK-3) are used if they are available and are equally appropriate for the purposes of the experiment.

3. Shotgun experiments. These experiments involve the production of recombinant DNAs between the vector and the total DNA (or preferably a partially purified fraction thereof) from the specified cellular source.

(a) Eukaryotic DNA recombinants—Primates, F3 physical containment—jan EK3 host-vector, or F4 physical containment—jan EK3 host-vector, except for DNA from untransformed embryonic cells from an individual cell line in which DNA from transformed embryonic cells for which F3 physical containment—jan EK3 host-vector can be used. The basis for the lower containment of the case DNA from the latter tissues (including cells of adult tissue) is the relative freedom from horizontally acquired adventitious viruses.

(b) Cold-blooded vertebrates. F2 physical containment—jan EK2 host-vector. Birds, F3 physical containment—jan EK2 host-vector.

(c) Cold-blooded vertebrates. F2 physical containment—jan EK2 host-vector except for DNA from amphibian cell lines which require F2 physical containment—jan EK2 host-vector. If the eukaryote is known to produce a potent toxin, the containment shall be increased to F2+EK2.

(d) Cold-blooded animals and lower eukaryotes. This large class of eukaryotes is divided into two categories: (1) those species that are known to produce a potent toxin, or are known pathogens (i.e., plant pathogens) or are known to carry such pathogenic agents must use F3 physical containment—jan EK2 host-vector. Any species that has a demonstrated capacity for carrying particular pathogenic agents is included in this group unless it has been shown that these organisms used as the source of DNA do not contain these agents; in this case they may be placed in the second group.

(2) The remainder of species in this class can use F2—EK2. However, any insect in this group should have been grown under laboratory conditions appropriate to its use as a source of DNA.

Plants. F2 physical containment—jan EK2 host-vector. Any plant carries a known pathogenic agent or makes a product known to be dangerous to any species, the containment must be raised to F3 physical containment—jan EK2 host-vector.

(i) Prokaryotes DNA recombinants—Probhage contains genetic information from E. coli.

The level of physical containment is directly determined by the rule of the most dangerous component (see introduction to Section III). Thus P1 conditions can be used for DNAs from those bacteria in Class 1 of ref. 5 ("Agents of no or minimal hazard * * "), which naturally exchange genetic information with E. coli, and P2 conditions should be used for such bacteria if they fall in Class 2 of ref. 5 ("Agents of ordinary potential hazard * * "), or plant pathogens or symbionts. EK1 host-vectors can be used for all experiments requiring biological containment; in fact, experiments in this category can be performed with E. coli K-12 vectors employing only those recombinant plasmids than EK1 vectors. Experiments with DNA from species requiring P2 physical containment require pathogen (e.g., enteropathogenic Escherichia coli, Salmonella typhimurium, and Klebsiella pneumoniae) can use EK1 host-vectors, but those of moderate biological containment (e.g., for example, Salmonella typhimurium, Shigella flexneri, type 1, and Vibrio cholerae) must use EK2 host-vectors. A specific example of an experiment with a plant pathogen requiring P2 physical containment—an EK2 host-vector would be cloning the tumor gene of Agrobacterium tumefaciens.

Prokaryotes that do not exchange genetic information with E. coli. The minimum containment conditions for this class consist of P2 physical containment—jan EK2 host-vector or P3 physical containment—jan EK2 host-vector, and when the risk that the recombinant DNA (i.e., increase the pathogen or ecological potential of the organism) is judged to be minimal. Experiments with DNA from non-pathogenic species (Class 2 of ref. 5) or host-vectors (P3-5 plus plant pathogens) must use P3-5-ECa. A specific example of an experiment with a pathogen requiring P2 physical containment—an EK2 host-vector would be cloning the tumor gene of Agrobacterium tumefaciens.

Prokaryotes that do not exchange genetic information with E. coli. The minimum containment conditions for this class consist of P2 physical containment—jan EK2 host-vector or P3 physical containment—jan EK2 host-vector, and when the risk that the recombinant DNA (i.e., increase the pathogen or ecological potential of the organism) is judged to be minimal. Experiments with DNA from non-pathogenic species (Class 2 of ref. 5) or host-vectors (P3-5 plus plant pathogens) must use P3-5-ECa. A specific example of an experiment with a pathogen requiring P2 physical containment—an EK2 host-vector would be cloning the tumor gene of Agrobacterium tumefaciens.

Prokaryotes that do not exchange genetic information with E. coli. The minimum containment conditions for this class consist of P2 physical containment—jan EK2 host-vector or P3 physical containment—jan EK2 host-vector, and when the risk that the recombinant DNA (i.e., increase the pathogen or ecological potential of the organism) is judged to be minimal. Experiments with DNA from non-pathogenic species (Class 2 of ref. 5) or host-vectors (P3-5 plus plant pathogens) must use P3-5-ECa. A specific example of an experiment with a pathogen requiring P2 physical containment—an EK2 host-vector would be cloning the tumor gene of Agrobacterium tumefaciens.
new condition is not less than that specified above for characterized clones from shotgun experiments (Section <i>&gt;&gt;</i>—III).

4. Plasmids, and other viruses. Recombinants formed between E. coli type vectors and other plasmid or virus DNAs have in certain cases been shown to be capable of replicating as a result of functions provided by the DNA inserted into the E. coli vectors. These are considered under other host-vector systems.

(i) Animal viruses. P3-+EK2 or P3-+EK3 shall be used to isolate DNA recombinants that include all or part of the genome of an animal virus. This recommendation applies not only to experiments of the "shooting" type but also to those involving partially characterized subgenomic segments of viral DNAs, (for example, the genome of defective viruses, DNA fragments isolated after treatment with restriction enzymes, etc.) When cloned recombinants have been shown by suitable biochemical and biological tests to be free of harmful regions, they can be considered to be isolated DNA.

(ii) In the case of DNA viruses, harmless regions include the late region of the genome; in the case of RNA viruses, the genome might include the coding regions for capsid proteins or envelope proteins.

(iii) Plasmid E. coli or P3-+EK2 conditions shall be used to form DNA recombinants that include all or part of the genome of a phage. These are classified according to whether or not the recombinants are formed from plasmids or phages that have not been characterized with regard to presence of harmful genes or are known to contribute significantly to the pathogenicity of their normal hosts. Moreover, if the DNA recombinants are formed from plasmids or phages that have known to contain harmful genes, the experiments can be performed with P1 physical containment conditions.

(iv) Prokaryotic plasmid and phage DNAs. Plasmids and phage from hosts that exchange genetic information with E. coli. Experiments with DNA recombinants formed from plasmids or phage genomes that have not been characterized with regard to presence of harmful genes or are known to contribute significantly to the pathogenicity of their normal hosts must use the containment conditions specified for shotgun experiments with the same organism.

If the DNA recombinants are formed from plasmids or phages that are known not to contain harmful genes, the experiments can be performed with P1 physical containment conditions. However, if the DNA recombinants are formed from plasmids or phages that are known to contain harmful genes, the experiments can be performed with P1 physical containment conditions.

Plasmids and phage from hosts that do not exchange genetic information with E. coli, The rules for shotgun experiments with DNA from the host apply to their plasmids or phages. The minimum containment conditions necessary for DNA recombinants formed from plasmids or phages of the risk that the recombinant DNA will increase the pathogenicity or ecological potential of the host are judged to be minimal.

Note: When applicable, cDNAs (i.e., complementary DNA molecules) synthesized in vitro from cellular or viral RNAs are included within each of the above classifications. For example, cDNAs formed from cellular RNAs that are not purified and characterized are grouped with those from the above experiments; cDNAs formed from purified and characterized RNAs are included under the appropriate conditions. cDNAs formed from viral RNAs are included under &gt;&gt;—III.

5. Experiments with other prokaryotic host-vectors.

(a) Other prokaryotic host-vectors. Other prokaryotic host-vector systems are similar to the specific, planning, and containment considerations given above for E. coli K-12 hosts. These do not warrant detailed treatment here at this time. However, the containment criteria require that the recombinants formed with E. coli K-12 host-vectors can, with the addition of some general guidelines provided here, serve as a guide for containment conditions. Given the similarity of functions provided by the DNA inserted into the E. coli vectors, these guidelines are applicable.

(b) Certain experimental organisms can be used for experiments with DNA recombinants. These are: E. coli K-12 host-vectors-for instance, thermostable organisms or other host-vectors whose habits do not include humans and/or economically important animals and plants. In general, the strains of any prokaryotic species used as the host is to conform to the definition of Class I etiological agents given in ref. (i.e., "Agents for no or minimal hazard * * * "), and the plasmid or phage vector should not make the host more hazardous. Appendix A gives a description of the containment systems, the most promising alternative to date.

At the initial stage, the host-vector must exhibit the following characteristics: (i) Biological containment comparable to EKI systems, and should be capable of modification to obtain high copy number; (ii) the host-vector has been characterized with regard to functions provided by the DNA inserted into the E. coli vectors. The type of transformation test(s) required to move a host-vector from an EKI-type classification to an EKl-type classification will depend on the unit replication of the host-vector. For example, if the unmodified host-vector propagates in its ecological niche, it should be consider equivalent to EKI and EKl. The type of transformation test(s) required to move a host-vector from a non-reverting, doubly integrated plasmid into a single copy plasmid or phage vector should not make the host more hazardous. Appendix A gives a description of the containment systems, the most promising alternative to date.

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(c) Certain experimental organisms can be used for experiments with DNA recombinants. These are: E. coli K-12 host-vectors-for instance, thermostable organisms or other host-vectors whose habits do not include humans and/or economically important animals and plants. In general, the strains of any prokaryotic species used as the host is to conform to the definition of Class I etiological agents given in ref. (i.e., "Agents for no or minimal hazard * * * "), and the plasmid or phage vector should not make the host more hazardous. Appendix A gives a description of the containment systems, the most promising alternative to date.

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(d) Eukaryotic organelle DNAs. The containment conditions given below apply only when the eukaryotic organelle DNA has been purified from isolated organelles or from eukaryotic DNA from plastids: P3-+EK1 or P3-+EK2. Mitochondrial or chloroplast DNA from other eukaryotic sources, DNA from plastids or viruses) are classified according to whether the recombinant DNA is formed with E. coli K-12 host-vectors or not, and the containment conditions given for these two classes with E. coli K-12 host-vectors with recombinants between plastid or phage vectors and DNA that extends the range of recombinant DNA that can be transferred to and propagate in, or on, or around plant hosts, or transmit recombinant DNA to other bacterial hosts that are able to carry out these ecological niches, and it is these lower probabilities which must be confirmed. The following principles are to be followed in the containment criteria given for experiments with E. coli K-12 host-vectors as a guide for other prokaryotic systems. Experiments with DNA from polyomavirus (and their plasmids or viruses) are classified according to whether or not the recombinants are formed from plasmids or phages that are known not to contain harmful genes, and characterized plasmid or phage DNA segments known not to contain harmful genes, the experiments can be performed with P1 physical containment conditions.

Plasmids and phage from hosts that do not exchange genetic information with E. coli, The rules for shotgun experiments with DNA from the host apply to their plasmids or phages. The minimum containment conditions necessary for DNA recombinants formed from plasmids or phage genomes that have not been characterized with regard to presence of harmful genes or are known to contribute significantly to the pathogenicity of their normal hosts must use the containment conditions specified for shotgun experiments with the same organism.

If the DNA recombinants are formed from plasmids or phages that are known not to contain harmful genes, the experiments can be performed with P1 physical containment conditions. However, if the DNA recombinants are formed from plasmids or phages that are known to contain harmful genes, the experiments can be performed with P1 physical containment conditions.

(c) The template regions for the major gene products.

(d) It should be well studied genetically. It is desirable that mutants be available in adequate number and variety, and that quantitative studies of recombination have been performed.

(e) The recombinant must be defective, that is its propagation is dependent upon the presence of a helper genome. This helper should either (a) be integrated into the genome of a stable line of host cells (a situation that would effectively limit the growth of the vector to the particular cell line) or (b) consist of a defective genome or an appropriate condition lethal mutant virus (in which case the experiments would be done under non-permissive conditions), making vector and helper dependent upon each other for propagation. However, if none of these is available, the use of a non-defective genome as helper would be acceptable.

Currently only two viral DNA's can be considered as meeting these requirements: These are the genomes of polyoma virus and SV40. Of these, polyoma virus is highly to be preferred. SV40 is known to propagate in human cells, both in vitro and in vivo, and to infect laboratory personnel, as evidenced by the presence of antibodies to SV40 in sera of many laboratory workers. SV40 shares many properties, and gives complementation, with the common human papova viruses. By contrast, we are not evidence that SV40 infects humans, nor does it replicate to any significant extent in human cells in vitro. However, this system still needs to be studied more extensively. Appendix B gives further details and documentation. Table 3 presents a summary of all these factors:

1. Polyoma virus. A Recombinant DNA molecules consisting of defective polyoma virus DNA, or segments of viral DNA from nonpathogen organism, including Class I viruses (5), can be propagated in or used to transform animal cells. In the absence of appropriate conditions are required. Appropriate helper virus may be used if needed. Whenever there is a choice, it is urged that mouse cells, derived preferably from embryos, be used as the source of eukaryotic DNA. Polyoma virus is a mouse virus and recombinant DNA molecules containing DNA from nonhuman cells is known to be present in virus stocks grown at a high multiplicity. Thus, recombinants formed in vitro between polyoma virus DNA

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and mouse DNA are presumably not novel from an evolutionary point of view.

b. Such experiments to be carried out under P4 conditions if the recombinant DNA contains sequences of the genomes of Class 2 animal or plant pathogens (6). Once it is has been shown by biologically active, plasmid DNA, that the cloned recombinant contains only harmless regions of the viral genome (see Section III-B-1) and that the polyoma virus vector has not been altered, experiments can be carried out under P3 conditions.

2. SV40 Virus. a. Defective SV40 genomes, with appropriate helper, can be used as a vector for recombinant DNA molecules containing sequences of any non-pathogenic organism or Class I viruses (5), (i.e., a, shotgun type experiment). P4 conditions are required. Established lines of cultured cells should be used.

b. Such experiments to be carried out in P3 (or P4) conditions if the non-SV40 DNA segment(s) is (a) a purified segment of prokaryotic DNA lacking toxogenic genes or (b) a segment of eukaryotic DNA whose function has been established, which does not code for a toxic product, and which has been previously cloned in a prokaryotic host-vector system. It shall be confirmed that the defective virus—helper virus system does not function efficiently in human cells in tissue culture than does SV40, following infection at a multiplicity of one or more helper SV40 virus per cell.

c. A recombinant DNA molecule consisting of defective SV40 DNA lacking subantigenic cellular element in established lines of cells under P3 conditions provided that there is no exogenous or endogenous helper, and that it is demonstrated that no infectious virus particles are being produced. Until this has been demonstrated, the appropriate containment conditions specified in 2. a. and 2. b. shall be used.

d. Recombinant DNA molecules consisting of defective SV40 DNA and sequences from non-pathogenic prokaryotic or eukaryotic organisms or Class I viruses (5) can be propagated as an autonomous cellular element in established lines of cells under P3 conditions provided that there is no exogenous or endogenous helper, and that it is demonstrated that no infectious virus particles are being produced. Until this has been demonstrated, the appropriate containment conditions specified in 2. a. and 2. b. shall be used.

The greenhouse facilities accommodating P2 laboratory physical containment conditions to be provided for greenhouses, (ii) appropriate sterilization of contaminated plants, pots, soil, and runoff water, and (iii) adoption of the other standard practices for microbiological work. P3 physical containment can be sufficiently approximated by confining the operations with infectious materials to a single laboratory, and by using those used for work with radioactive isotopes: Provided, That (i) such chambers are modified to produce a negative pressure environment with the exhaust air appropriately filtered, (ii) that other operations with infectious materials are carried out under the specified P3 conditions, and (iii) to guard against inadvertent transmission of recombintant DNA, growth rooms shall be routinely fumigated and only used in insect-proof rooms. The P2 and P3 conditions specified earlier are therefore extended to include these cases for work on higher plants.

The host cells for experiments on recombintant DNAs may be cells in culture, in seed or plant parts. Whole plants or plant parts that cannot be adequately contained shall not be used as hosts for shotgun experiments at this time, and attempts to infect whole plants with recombinant DNA need not be initiated until the experiments on host cells in which plant parts have been thoroughly studied.

Organelle or plasmid DNAs and DNAs of viruses or retroviruses may be used as vectors. In general, similar criteria for selecting host-vectors to those given in the preceding section on animal systems are to apply to plant systems.

DNA recombinants formed between the initial moderately contain vectors and DNA from non-pathogenic species in which the vector DNA can replicate, require P2 physical containment. Otherwise, if the source of the DNA is itself pathogenic or known to carry pathogenic agents, or to produce products dangerous to plants, or if the vector is an unmodified virus of unrestricted host range, the experiments shall be carried out under P3 conditions.

Experiments on recombinant DNAs formed between the above vectors and DNAs from other species can also be carried out under P3 if the DNA has been purified and determined not to contain harmful genes. Otherwise, the experiments shall be carried out under P3 conditions if the source of the recombinant DNA is itself pathogenic or known to carry such pathogenic agents, or to produce harmful products—and under P4 if the source of the recombinant DNA is not known to carry such pathogenic agents.

The development and use of host-vector systems that exhibit a high level of biological containment will require release of one step in the bacterial containment system specified above (P4—P3—P2—P1) or similar lower eukaryotic host-vector systems. The containment criteria for experiments on recombinant DNAs using these host-vectors most closely resemble those for recombinant DNAs, rather than those for the preceding eukaryotes, in that the host cells usually exhibit a capacity for whole plant growth, and are similar to that for bacteria. We therefore consider that the containment guidelines given for E. coli 5, and other prokaryotic host-vectors (Sections III-B-1 and -2, respectively) provide adequate direction for experiments with these lower eukaryotic systems. This is particularly true at this time since the development of these host-vectors is presently in the speculative stage.

IV. ROLES AND RESPONSIBILITIES

Safely in research involving recombinant DNA molecules depends upon how the research team applies these guidelines. Motivation and critical judgment in addition to specific safety knowledge, to ensure protection of personnel, the public, and the environment.

The guidelines given here are to help the principal investigator determine the nature of the safeguards that should be implemented. These guidelines will be incomplete in some respects because all conceivable experiments with recombinant DNAs cannot now be anticipated. Therefore, they cannot substitute for the investigator's own knowledgeable and discriminating evaluation. Whenever this evaluation calls for an increase in containment over that indicated in the guidelines, the investigator has a responsibility to institute such an increase.

In contrast, the containment conditions called for in the guidelines should not be decreased without review and approval at the institutional and NIH levels.

The following roles and responsibilities define an administrative framework in which safety is an essential and integrated function of research involving recombinant DNA molecules.

1. Principal Investigator. The principal investigator has the primary responsibility for (i) Determining the real and potential biohazard of the proposed research; (ii) determining the appropriate level of biological containment; (iii) selecting the microbiological practices and laboratory techniques for handling recombinant DNA materials; (iv) preparing procedures for dealing with accidental spills and overt personnel contamination, (v) determining the applicability of various precautionary medical practices, serological monitoring, and immunization, when available, (vi) securing approval of the proposed research prior to initiation of work, (vii) submitting information on purported EB2 and EC2 systems to the NIH Recombinant DNA Molecule Program Advisory Committee and making the strains available to others, (viii) reporting to the institutional biohazards committee and the NIH Office of Recombinant DNA Activities new information bearing on the guidelines, such as technical information relating to hazards and new safety procedures or inventions; (ix) applying for approval from the NIH Recombinant DNA Molecule Program Advisory Committee for large scale experiments with recombinant DNA molecules within the scope of the approved grant, and (x) applying to NIH for approval to lower containment levels when a cloned DNA sequence derived from a shotgun experiment has been rigorously characterized and there is sufficient evidence that it is not novel.

Before work is begun, the principal investigator is responsible for: (i) Making available to program and support staff copies of these portions of the approved grant application that describe the biohazards and the precautions to be taken, (ii) advising the program staff and support staff of the nature and assessment of the real and potential biohazards, (iii) instructing and training the support staff in the practices and techniques for handling recombinant DNA materials to ensure safety, and in the procedures for dealing with accidentally created biohazards, and (iv) informing the NIH and the institutional biohazards committee of any additional or requested precautionary medical practices, vaccinations, or serum collection.

During the conduct of the research, the principal investigator is responsible for: (i)
Supervising the safety performance of the staff to ensure that all procedures and techniques are employed, (ii) investigating and reporting in writing to the NIH Office of Recombinant DNA Activities and appropriate institutional biosafety committees any serious or extended illness of a worker or any accident that results in (a) inoculation or exposure to materials that may cause cutaneous penetration, (b) ingestion of recombinant DNA materials, (c) inhalation of recombinant DNA materials, following gross aerosolization, or (d) any incident causing serious exposure to personnel or danger of environmental contamination, (iii) investigating and reporting in writing to the NIH Office of Recombinant DNA Activities and the appropriate institutional biosafety committees any problems pertaining to operation and implementation of biological and physical containment safety practices and procedures, or equipment or facility failure, (iv) correcting work errors and conditions that may result in the release of recombinant DNA materials, and (v) assuring the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment of recombinant DNA materials throughout the laboratory and in any facilities in which recombinant DNA materials are being handled, assuring that (a) protective genotypic and phenotypic characteristics, purity, etc., are maintained in recombinant DNA molecules resulting from different genetic segments of DNA that have been joined together in cell-free systems, the capacity to infect and replicate in some host cell either autonomously or as an integrated part of their host's genome, on the development of procedures which are designed to prevent the spread of such molecules within human and other populations, and on guidelines to be followed by investigators working with potentially hazardous recombinants.

The NIH Recombinant DNA Program Advisory Committee (RAC) is appointed by the Director of the National Institutes of Health, and the RAC has responsibility for: (i) Revising and updating guidelines to be followed by investigators working with recombinant DNA materials; (ii) for the time being, receiving information on purported EK2 and EK3 systems and evaluating and certifying that host-vector systems meet EK2 or EK3 criteria; (iii) reviewing questions concerning potential biohazard and adequacy of containment capability if NIH staff or NIH investigators are involved; (iv) reviewing and approving large scale experiments with recombinant DNAs known to make harmful products (e.g., more than 10 liters of culture).

The bacteria which constitute Class 2 of ref. 5 ("Agents of ordinary potential hazard . . .") represent a broad spectrum of etiologic agents which possess different levels of virulence and degrees of communicability. We think it appropriate for our specific purpose to divide these bacteria into two classes. The following specific example may serve to illustrate the principle.

The term "characterized" and "free of harmful genes" are unavoidably vague. But in this instance, before containment conditions lower than the ones used to clone the DNA can be adopted, the investigator must obtain approval from the National Institute of Health. Such approval would be contingent upon data concerning: (a) The absence of potentially harmful genes (e.g., sequence...
markedly reduced. Thus, the probability of cloning a harmful gene, for example, by reducing its probability by more than 10-fold when a non-repetitive gene from mammals was being sought. Furthermore, the fact of purity specified here makes it easier to establish that the desired DNA does not contain harmful genes.

"The DNA preparation is defined as purified if the desired DNA represents at least 99 percent (w/w) of the total DNA in the preparation. It was verified by more than one procedure."
NIGHTINGALE.

SETLOW, Jane

ROWE, John, Ph.D., Member and Chairmen of the Department of Microbiology, Scripps Clinic and Research Foundation (11). The most extensively studied members of the S. subtilis genoscope include B. amyloliquefaciens, B. lentiformes, B. purpuraniger, B. subtilis, and B. thuringiensis (refer to reference 12 for a review and references 3-15 for examples of this heterologous exchange). This exchange occurs efficiently and there is a surprisingly wide discrepancy between DNA-DNA hybridization among these organisms (16). Even though the frequency of transformation is low in the heterologous cross (e.g., B. amyloliquefaciens (donor) × S. subtilis (recipient)), the newly acquired DNA from B. amyloliquefaciens in the S. subtilis background can be readily transferred at high efficiencies to other recipient strains of S. subtilis (14). Therefore, the extremely high frequency of transformation permits the recognition and selection of rare events.

D. Current and potential vectors for recombinant molecular experiments. Lovett and coworkers have recently described cryptic plasmids in S. subtilis (18). Of these organisms, S. subtilis ATCC 7003 appears to be the most useful since it contains a plasmid with a molecular weight of 40 X 10^6. This strain is also closely related to S. subtilis 168. Another strain of S. subtilis (ATCC 4841) contains 16 copies of a plasmid with a molecular weight of 4.5 X 10^6. Currently, it is not known whether genes can be readily incorporated into these plasmids. To date, it has not been possible to readily stabilize plasmids derived from S. purpureus or S. subtilis. Perhaps the heavy selective pressure (P. Lovett, personal communication).

Two temperate bacteriophages are under development in S. subtilis, 4X7 and SP02. Lysogeny of thymine auxotrophs can readily be assayed on a Tg phenotype. The attachment site for this bacteriophage and the bacteriophage gene for thymidylate synthetase (thyp) map between the bacterial thyt and thyD loci in the terminal region of the chromosome of S. subtilis (19). The viral genome is readily transducible in S. subtilis and B. subtilis. In B. subtilis, Bam 1 (20), to produce 5 fragments (one of which carries the thyp gene). The thyp gene is also transduced into the bacterial genome in the absence of the intact viral genome. Because deletions are available that inactivate one or both termini, it is theoretically possible to introduce thyp at many sites on the chromosome. The thyp gene can be readily purified from bacteriophage into other heterologous DNA into the chromosomes of S. subtilis. Alternatively, it is possible to purify fragments of the chromosome by gel electrophoresis (21, 22), for insertion into bacteriophage 4X7 or SP02. At present, unfortunately, only the bacterial marker can be used as a selectable marker, i.e., the gene for thymidylate synthetase, thyp.

G. Developing vehicles. S. subtilis is a Gram-positive sporulating rod that usually lacks endotoxin in the cell wall. Therefore the cells can be used as a single cell protein source.

H. The frequency of transformation is very high, facilitating the detection of rare events.

I. A unique bacteriophage, 4X7, exists that carries a gene that can be readily purified for "recombinant" molecular experiments.

II. Disadvantages. 1. The knowledge of genes and physiology of plasmids and viruses is at present rudimentary.

2. High-frequency, specialized transduction is not available as a means of gene transfer.

Based on its promise, it seems appropriate, and not chauvinistic, to urge development of the S. subtilis system-a. Advantages. 1. S. subtilis is nonpathogenic. Asporogenic deletion mutants are available to preclude the problem of persistence through sporulation.

2. The circular chromosomal map is well defined. At least 16 loci have been positioned.

3. The organism is commercially important in the fermentation industry.

4. The numbers of organisms can be dispersed of readily with minimal environmental impact.

5. Unlike E. coli, it lacks endotoxin in the cell wall. Therefore the cells can be used as a single cell protein source.

6. The frequency of transformation is very high, facilitating the detection of rare events.

7. A unique bacteriophage, 4X7, exists that carries a gene that can be readily purified for "recombinant" molecular experiments.

8. The virus is at present rudimentary.

9. Asporogenic deletion mutants are available to preclude the problem of persistence through sporulation.

References


APPENDIX B TO APPENDIX D

POLYOMA AND SV40 VIRUS

Polyoma virus is a virus of mice, and infection with wild mouse populations is a common event, for the virus has often been isolated from a high proportion of healthy adult animals, both wild and laboratory bred, of many colonies (Gross, L, Proc. Soc. Exp. Biol. 68, 283-286, 1958; Rowe, W. F., Proc. Nat. Acad. Sci. USA 52, 18-31, 1961). As far as is known, the virus almost never causes a disease in these animals. However, when large quantities of the virus are administered to newborn or suckling mice or hamsters, a variety of solid tumors is induced (Gross, L. Oncogenesis and Tumors, Second Edition, Furtan Press, NY).

Polyoma virus grows lytically in mouse cells in tissue culture. Thus mouse cells in culture are probably transformed only by virus particles that contain certain kinds of defective genes. Cells of other rodent species, however, can be transformed by polyoma virus particles that contain complete genomes (Folk, W. J. Virol. 41, 424-421, 1973). The virus does not replicate to a significant extent in human cells in tissue culture (Eddy, B.E., Virol. Monogr. 1, 1-114, 1969; Pollack, R., Biochim. Biophys. Acta 126, 177-179, 1967). The resistance of the cells seems to be a consequence of the failure of the virus to absorb or uncoat. However, even when naked viral DNA is introduced into the cells only an abortive cycle of replication ensues; early viral proteins are made, there is induction of cellular DNA synthesis, but no expression of late viral protein is detected. Stable infections are established only in their established only in their rat cells. (Ober, A., U. Magerras, and K. Gross, J. Virol. 20, 117-120, 1971). The resistance of the cells seems to be a consequence of the failure of the virus to absorb or uncoat. However, even when naked viral DNA is introduced into the cells only an abortive cycle of replication ensues; early viral proteins are made, there is induction of cellular DNA synthesis, but no expression of late viral protein is detected. Stable infections are established only in their established only in their rat cells. (Ober, A., U. Magerras, and K. Gross, J. Virol. 20, 117-120, 1971).

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There is no evidence that polyoma virus can infect other mammals, to our knowledge. The virus can now be grown in large quantities in tissue culture; some of the virus is used to complement the growth of certain temperature-sensitive mutants of SV40 (Mason, D. H. and Takemoto, K. E., submitted for publication).

FURTHER WORK

At present, a potential cutaneous vector of choice is polyoma virus. And while available information indicates that it fulfills all the necessary criteria, we recommend that the following subjects be further investigated:

1. The molecular mechanism of resistance of human cells to the virus.
2. The extent of heterology between polyoma virus DNA and the DNAs of human papovaviruses.
3. The ability of human papovaviruses to complement defective polyoma virus genomes.

Report of a Working Group Consisting of:
Dr. Bernard Fields, Harvard University School of Medicine.
Dr. Thomas J. Kelly, Jr., Johns Hopkins University School of Medicine.
Dr. Andrew Lewis, National Institute of Allergy and Infectious Diseases.
Dr. Malcolm Martin, National Institute of
Allergy and Infectious Diseases. Dr. Robert Martin, National Institute of Arthritis, Metabolism, and Digestive Diseases.

Dr. Elmer Pfefferkorn, Dartmouth Medical School.

Dr. Wallace P. Rowe, National Institute of Allergy and Infectious Diseases.

Dr. Aaron Seshkin, Roche Institute of Molecular Biology.

Dr. Maxine Singer, National Cancer Institute.

Rapporteur: Dr. Joe Sambrook, Cold Spring Harbor.

APPENDIX C TO APPENDIX D

SUMMARY OF THE WORKSHOP ON THE DESIGN AND TESTING OF SAFE PHAGE VECTORS AND BACTERIAL HOSTS FOR RESEARCH ON RECOMBINANT DNA MOLECULES

Torrey Pines Inn, La Jolla, California

The development of techniques for the cloning of DNA from both prokaryotic and eukaryotic organisms in bacteria has had great impact on research in biology and medicine and promises extraordinary social benefits. The biohazards involved in the use of this technology in many instances are very difficult to assess. For this reason, codes of practice are being formulated in the United States and other countries for the conduct of these experiments that might produce a potential biohazard. One of the requirements for conducting such cloning experiments is the use of safer vector (bacteriophage or plasmid) systems that have restricted capacity to survive outside of controlled conditions in the laboratory. Approximately sixty scientists from the United States and several foreign countries participated in a workshop on the Design and Testing of Safer Prokaryotic and Bacterial Vectors and Hosts for Research on Recombinant DNA Molecules at La Jolla, California, on December 1 to 3, 1976. The workshop was sponsored by the Research Resources Branch of the National Institute of Allergy and Infectious Diseases. The purpose of the meeting was the exchange of recent data on the development of safer prophage host-vector systems, devising methods of testing the level of containment provided by these systems and exploring the various directions that future research should take in the construction of safer bacterial systems for the cloning of foreign DNA.

The first session of the workshop, chaired by W. Snyder of Wisconsin, was devoted to bacteriophage vectors. Synder outlined the main safety features of the two-component, phage-bacterium system, in which the host bacteria offer the safety feature of not carrying the cloned DNA, and the phage vectors cannot be propagated in the absence of an appropriate host. There are two primary escape routes for the clones of foreign DNA carried by the phage vector: (1) establishment of a stable prophage in the host cell, and (2) escape of the phage vector. Escape of the phage vector carries the cloned DNA and its subsequent productive encounter with a suitable host in the natural environment. The general consensus was that to ensure safety, both routes should be blocked by selecting for appropriate mutations. For phage λ, route (1) can be blocked by phage mutations that interfere with lysogenization (e.g., 431, aO or aK), and route (2) is blocked by prophage formation (Nϕ, miniR, ϕ6, ϕ4, ϕ4Y, ϕ6, ϕ4, ϕ4t, ϕ4s, and ϕ6) and by mutations in the Escherichia coli chromosome that affect these processes (attB, dmcA100s) and host survival. Route (2), (which is of low probability since λ phages do not survive well in natural environments) can also be blocked after phage infection: if 10^5 to 10^6 particles, are killed by desensitization, and have a low chance to encounter a naturally sensitive host) can be blocked further by the following phage modifications: (a) mutations which result in extreme instability of the plaques under all conditions other than those specially designed for phage propagation in the laboratory (e.g., by substitution of a drug resistance or some other compound), or (b) employing phage vectors in which the tail genes are deleted. It was suggested that (i) only the DNA-packed heads; only under laboratory conditions could such heads be made transiently infectious by allowing them with separately prepared tails. The high instability of the phage would minimize the possibility of transfer of the cloned genome into receptive bacteria found in nature. Moreover, the propagation of the phage can be blocked by many conditional mutations, which would be designed to block any secondary route of escape, mainly depending on transfer of the cloned DNA into another phage host. It was recommended further that the vector be designed in such a manner as to permit easy infection and monitoring of the foreign DNA and rapid assay of the safety features and give a high yield of cloned DNA (not less than 10^6 molecules per ml). In addition, the vector should contain a selectable marker (e.g., a chromosomal or extrachromosomal genetic information; (d) poorly recombines or does not recombine with the chromosome of the host cell; (e) provides no selective advantage to the host cell for carrying the plasmid; the collective property is conditional; and (f) possesses mutations that restrict its maintenance as a replication-deficient plasmid) that could be used as a plasmid vector.

Synder and S. Brener (Cambridge University) stressed that research on recombinant DNA molecules may lend itself to very simple and inexpensive mechanical containment approaches. The containment box, since all the vectors that carry such recombinant molecules possibly can be both created and destroyed in such a box, while development of special methods might permit study of many properties of the recombinant DNA, without ever removing it from the box. These safety features were reflected in the subsequent presentations by C. Blattner and W. Williams (University of Wisconsin) described four specially constructed λ-23 phages which incorporate all of the safety features, and which they named Charon phages, for the mythical boatman of the river Styx. Some of these highly converted phages do not form prophage (e.g., mini-r, mini-R). D. Davis, J. Cameron, and K. Struhl (Stanford University) found that λ phages carrying the recA mutation could (i) not be amplified as well as the parental vector, which could select against their survival in nature. They also showed that some mutations could be expressed in E. coli, partially compensating for deficiencies in the histidine pathway in a his- or his* functions. These investigators over 1000 strands of E. coli isolated in the natural environment and did not find a single one that could support growth of either the λ vector.

V. Bode (Kansas State University) described a replica plating method which precisely detects the fraction of λ vectors carrying CoE1 or CoE1 derivatives (mini-CoE1-ham and mini-CoE1-trp) as cloning vehicles. Finally, she described the temperature-sensitive property of trp and ham derivatives of a temperature-sensitive replication mutant of λ (R. Roeder, M. Williams, and H. Boyer) which resulted in the development of a mini-CoE1 plasmid and derivatives of this plasmid (mini-CoE1-trp and mini-CoE1-ham) as cloning vehicles.

The second session of the workshop was devoted to bacterial vector systems. Some of the approaches are being formulated in the United States, and several foreign countries are participating in a workshop on the Design and Testing of Safer Prokaryotic and Bacterial Vectors and Hosts for Research on Recombinant DNA Molecules at La Jolla, California, on December 1 to 3, 1976. The workshop was sponsored by the Research Resources Branch of the National Institute of Allergy and Infectious Diseases. The purpose of the meeting was the exchange of recent data on the development of safer prophage host-vector systems, devising methods of testing the level of containment provided by these systems and exploring the various directions that future research should take in the construction of safer bacterial systems for the cloning of foreign DNA.

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described the properties of a variety of plasmids isolated from *Pseudomonas putida*. These plasmids, isolated from the prokaryotic host *Pseudomonas putida*, naturally exhibit unusual genetic characteristics. The plasmids isolated from *Bacillus megaterium* by E. Carlton (University of Georgia) from *E. coli* subtilis, and other naturally occurring *Bacillus* species by W. Goebel and K. Bernhard (Seattle Children’s Hospital), were discussed and their further development as plasmid-host cloning systems was explored. It was clear from these presentations that considerable progress has been made recently in the identification and characterization of a variety of plasmid elements that occur naturally in *Pseudomonas* and *Bacillus* species. Several of the plasmids described showed considerable promise as plasmid cloning systems involving a host other than *E. coli*.

A third session on the ecology and epidemiology of vector-host systems was chaired by S. Falkow (University of Washington). This workshop emerged, in part, from expressed fears that microorganisms containing conjugative plasmids potentially pose a threat to health or disrupt the normal ecological chain in some manner. Consequently, this session was devoted to currently available information on the ecology and epidemiology of *E. coli* and related bacterial species since it was recently noted that *E. coli* K-12, the prokaryotic host most commonly employed in the cloning of DNA molecules in the immediate future, F. Griswold (Scribner Reference Center, Copenhagen) reviewed the state of *E. coli* serotyping and what has been learned about the distribution of *E. coli* types in health and disease. Only certain *E. coli* types are generally recognized as good colonizers of the human gut and such strains come from a handful of the 160 well defined O (lipopolysaccharide) antigen types and 200 variable K (acetyl polysaccharide capsule) antigens. Some serotypes apparently have been disseminated worldwide and possibly represent the proliferation of a bacterial clone because of, as yet unknown, selective pressures. In contrast, *E. coli* K-12 has no detectable O or K antigens and is considered to be rough. This may account, at least in part, for its demonstrated poor ability to colonize the human or animal gut.

However, F. Freter (University of Wisconsin) pointed out that *E. coli* K-12 still remain largely ignorant of the factors which control intestinal *E. coli* populations. Freter also noted that while adherence to the mucosal surface of the small intestine is important in the pathogenesis of *E. coli* diarrheal disease, the "normal" intestinal microflora results in the evasion between a mammalian host and bacterium is established in the cecum and colon. It is in these locations that factors come into play to determine whether an *E. coli* strain passing through the intestine will become successfully implanted or whether it will be quickly eliminated in the feces. The factors controlling implantation include competition for substrates, inhibitors and the physiological state of the host. The large bowel, for example, ingests *E. coli* previously grown under usual laboratory conditions, and cells of the *E. coli* strain "pre-adapted" in a pH, Etc., often colonize well. Freter has developed a continuous culture system in which the strain can be used to study the uptake of plasma membrane precursors and is now testing the effects of plasma on the cell surface. Although it does revert at frequencies of $10^{-4}$ to $10^{-5}$, the mutation conferring bile salt sensitivity was obtained after Met-1 infection of an HR5 host which would result in the selection of an HR5 strain carrying recombinant DNA molecules. It was clear from these presentations that considerable progress has been made recently in the identification and characterization of a variety of plasmid elements that occur naturally in *Pseudomonas* and *Bacillus* species. Several of the plasmids described showed considerable promise as plasmid cloning systems involving a host other than *E. coli*.

The fourth session of the workshop, chaired by C. Curtiss III (University of Alabama), was concerned with the construction of safer bacterial hosts for DNA cloning. The goals in constructing safer host strains enumerated at this session included: (a) introduction of mutations that would: (a) Preclude colonization in normal ecological niches; (b) cause wall biosynthesis except in specially defined media; (c) cause degradation of genetic information in normal ecological niches; (d) cause vectors to be lost or eliminated during transmission of recombinant DNA to other strains in normal ecological niches; (f) increase usefulness of DNA molecule research; and (g) permit monitoring.

Most of the progress in developing safer hosts has been achieved with *E. coli* K-12, although F. Young described a *E. coli* subtilis strain with a deletion for sparo genes. Thus, a new strategy for constructing and testing new DNA vectors, which may be useful only with a phage vector, which has yet to be developed and/or discovered.

A. I. Bukhari (Cold Spring Harbor Laboratory) described the use of the dapD8 mutation in *E. coli* as a means of producing a functional *E. coli* strain which would allow the production of an alfalfa-mosaic virus which, although defective, would not reduce strain titers in feces. Strains with *E. coli* mutations also exhibited thymidylate death in vivo tests. Since strains with dapD8 allele can revert to *Dap* strains were constructed with both dapD8 and *Abilol*-and mutations. These strains have not been observed to revert to *Dap* but can survive passage through the rat intestine and in growth media lacking dianisopino acid but containing NaCl and 0.5% usable carbon sources. This survival was due to the introduction of these plasmids and *prokaryotic* host cells by *E. coli* K-12 sublines which offer a significant hazard as a potential enteric pathogen. This survival was due to the introduction of these plasmids and *prokaryotic* host cells by *E. coli* K-12 sublines which offer a significant hazard as a potential enteric pathogen.
SUPPLEMENTARY INFORMATION ON PHYSICAL CONTAINMENT

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APPENDIX D TO APPENDIX D

NOTICES

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
II. UNIVERSAL BIOHAZARD WARNING SYMBOL (1)
The biological hazard warning symbol (biohazard symbol) specified herein shall be used to signify the actual or potential presence of a biohazard and to identify equipment, containers, rooms, materials, experimental animals or combinations thereof which contain or are contaminated with viable hazardous agents.
The biohazard symbol shall be designed and proportioned as illustrated here:

![Biohazard Symbol]

The symbol shall be as prominent as practicable, and of a size consistent with the size of the equipment or material to which it is affixed, provided the proportions shown above are maintained, and, in any case, that the symbol can be easily seen from as many directions as possible.

Except when circumstances do not permit, the symbol shall be oriented with one of the three open circles pointed up and the other two forming a base.
The symbol color shall be a fluorescent orange or orange-red color. Background color is optional as long as there is sufficient contrast for the symbol to be clearly defined.

III. LABORATORY TECHNIQUES FOR BIOHAZARD CONTROL

A. Pipetting
1. No infectious or toxic materials should be pipetted by mouth (2, 3, 4).
2. No infectious mixtures should be prepared by bubbling a gasified air through a liquid with a pipette (2, 3, 4).
3. No infectious material should be blown out of pipettes (2, 3, 4).
4. Pipettes used for the pipetting of infectious or toxic materials should be plugged with cotton (2, 3, 4).
5. Contaminated pipettes should be placed horizontally in a pan containing enough suitable disinfectant to allow complete immersion (2, 3, 4). They should not be placed vertically in a cylinder.
6. The pan and pipettes should be autoclaved as a unit and replaced by a clean pan with fresh disinfectant (2, 3, 4).
7. Infectious material should not be mixed by alternate suction and expulsion through a pipette (2, 3, 4).
8. Mark-to-mark pipettes are preferable to other types, as they do not require expulsion of the last drop (6).
9. Discharge should be as close as possible to the fluid or agar level, or the contents should be allowed to run down the wall of the tube or bottle whenever possible—never dropped from a height (9).
10. A disinfectant-wetted towel over the immediate work surface is useful in some cases to minimize the splash from accidental droppage (9).

B. Syringes and Needles
1. To lessen the chance of accidental injection, aerosol production or spills, avoid unnecessary use of the syringe and needle. For instance:

   (i) Use the needle for parenteral injections but use a blunt needle or a cannula on the syringe for oral or intranasal inoculations.

   (ii) Do not use a syringe and needle as a substitute for a pipette in making dilutions of dangerous fluids.

   (ii) Use the syringe and needle in a Biological Safety Cabinet only and avoid quick and unnecessary movements of the hand holding the syringe.

   (iii) Discard syringes into a pan of disinfectant, preferably a disposable unit (a needle-locking type) syringes only, and be sure that the needle is locked securely into the barrel. A disposable syringe-needle unit (where the needle is an integral part of the unit) is preferred.

   (iii) Wear surgical or other type rubber gloves for all manipulations with needles and syringes.

   (iii) Fill the syringe carefully to minimize air bubbles and frothing of the inoculum.

   (iii) Expel excess air, liquid and bubbles from a syringe vertically into a cotton pledget moistened with the proper disinfectant, or into a small bottle of sterile cotton.

   (iii) Do not use the syringe to expel forcefully a stream of infectious fluid into an open vial or tube for the purpose of mixing. Mixture with a syringe is condemned only if the tip of the needle is held below the surface of the fluid in the tube.

   (iii) If syringes are filled from test tubes, take care not to contaminate the hub of the needle, as this may result in transfer of infectious material to the fingers.

   (iii) When removing a syringe and needle from a rubber-stoppered bottle, first withdraw the needle and stopper in a cotton pledget moistened with the proper disinfectant. If there is danger of the disinfectant contaminating sensitive experiments, a sterile pledget may be used and discarded immediately into disinfectant solution.

   (iii) Inoculate animals with the hand "behind" the needle to avoid punctures.

   (iii) Be sure the animal is properly restrained prior to the inoculation, and be on the alert for any unexpected movements of the animal.

   (iii) Before and after injection of an animal, swab the site of injection with a disinfectant.

   (iii) Discard syringes into a pan of disinfectant without removing the needle. The syringe first may be wiped with disinfectant by immersing the needle and slowly withdrawing the plunger, and finally removing the plunger and placing it separately into the disinfectant.

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   (iii) If syringes are filled from test tubes, take care not to contaminate the hub of the needle, as this may result in transfer of infectious material to the fingers. Autoclave syringes and needles in the pan of disinfectant.

   (iii) Use separate pans of disinfectant for disposable and nondisposable syringes and needles to eliminate a sorting problem in the service area.

   (iii) Do not discard syringes and needles into pans containing plates or other glassware that must be sorted out from the syringes and needles.

   (iii) Opening Culture Plates, Tubes, Bottles, and Ampoules

   1. Plates, tubes and bottles of fungit may release spores in large numbers when opened. Such cultures should be manipulated in a biological safety cabinet (6, 15).

   2. In the absence of definite accidents or obvious spillage, it is not certain that opening of plates, tubes and bottles of other microorganisms has caused laboratory infection. However, it is probable that among the highly Infective agents, some infections have occurred by this means and are represented in the 90% for which no known act or accident is ascribable (3).

   3. Water of syneresis in petri dish cultures is usually infected and forms a film between the rim and lid of the inverted
plate. Aerosols are dispersed when this film is broken by opening the plate. Vented plastic petri dishes with loose lids trapped at the rim at only three points are less likely to offer this hazard (8,19).

3. The risk may also be minimized by using properly dried plates, but even these (when incubated anaerobically) are likely to be wet. Although this practice is a simple device has been recommended, one less well appreciated fact is worth of mention. Celluloid tubes (plastic) are not less resistant to accidental breakage. This practice also provides an excellent cushion against abrasion that might otherwise create a hazard (10).

4. Avoid decanting centrifuge tubes. If you must do so, afterwards wipe off the outer rim of the tube. The inoculating or dispersive fluid will op slip off as an aerosol (4, 10).

5. Avoid filling the tube to the point that the rim, cap or cotton plug ever becomes wet with culture (4, 10).

6. Scrap caps, or caps which slip over the rim outside the centrifuge tube are safer than plug-in closures. Some fluid usually collects between a plug-in closure and the rim of the tube. Even filter-capped bottles are not without risk; however, if the rim is soiled some fluid will escape down the outside of the tube. Screw-capped bottles may jam in the bucket, and removing them is hazardous. Protecting such bottles higher in the bucket with additional rubber cushions is mechanically unsound (8).

7. Kitchen foil is often used to cap centrifuge tubes. This creates more risk than the screw cap. Foil caps often become detached in handling and centrifuging (6).

8. The test tube in a preliminary often mismanaged. Care must be taken to ensure that matched sets of trunnions, buckets and plastic inserts do not become mixed. If the caps of matched sets of trunnions and inserts are not without risk; however, if the rim is soiled some fluid will escape down the outside of the tube. Screw-capped bottles may jam in the bucket, and removing them is hazardous. Protecting such bottles higher in the bucket with additional rubber cushions is mechanically unsound (8).

9. Kitchen foil is often used to cap centrifuge tubes. This creates more risk than the screw cap. Foil caps often become detached in handling and centrifuging (6).

10. Fill and open centrifuge tubes or trunnion caps in a Biological Safety Cabinet (9).

11. High-Speed Centrifuges (22). 1. In high-speed centrifuges the bowl is connected to a vacuum pump. If there is a breakage or accidental dispersal of infected particles the pump may become contaminated. A high efficiency filter should be placed between the centrifuge and the pump (5).

12. Polypropylene jars are prone to metal fatigue, and where there is a chance that they may be used on more than one machine, an expensive companion equipment may be saved by its own log indicating the number of hours run at top or de-rated speeds. Failure to observe this precaution can result in dangerous and expensive disintegration. Frequent inspection, cleaning, and monitoring are important to ensure absence of corrosion or other contaminants which may lead to crevice corrosion. Rubber O-rings and tube closures must be examined for deterioration and be purplish lubricated and recirculated recommended by the manufacturer. Where tubes of different materials are provided (e.g., celluloid, polyethylene) care must be taken—these tubes closed specifically for the type of tube in use are inaccessible to cross contamination in similar appearance, but are prone to leakage if applied to tubes of the wrong material. When properly designed tubes and rotors are well maintained and handled, holding should never occur (6).

13. Before centrifuging, inspect tubes for cracks, and keep the inside of the trunnion cup for rough walls caused by erosion or adhering matter, and carefully remove bits of glass from the rubber cushion (4,10).

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nose of dried material. Whenever possible, ampoules should be filled with dry nitrogen after freezing or autoclaving and stored in a refrigerator or freezer until needed. If necessary, an impression that may occur during the sealing as well as opening of evacuated ampoules. The whole process of filling should be performed in the laboratory in a Biological Safety Cabinet. Filtration of the effluent air from the vacuum system is desirable (preferably) or, in the absence of such equipment, by: 4. To ensure that all virulent fluid cultures or viable powdered infectious material are glass vessels should be used. In easily handled, nonbreakable leak-proof containers that are large enough to contain all the fluid or powder in case of leakage or breakage of the glass vessel (4,10).

5. All inoculated petri plates or other incriminated solid media should be carefully packed and incubated in leak-proof pans or leak-proof containers (4,10).

6. Care must be exercised in the use of membrane filters to obtain sterile filtrates of infectious material. Because of the fragility of the membrane and other factors, such filters cannot be handled as noninfectious until culture or other tests have proved their sterility (4,10).

7. Shaking. Microbial cultures must be examined carefully for potential breakage of flasks or other containers being shaken. Screw caps or detachable plugs are recommended and should be used. These should be securely fastened to the shaker platform. An additional precaution is to place the flask in a plastic bag with or without an absorbent material.

8. No personnel should work alone on an extremely hazardous operation (4,10).

IV. PERSONAL HYGIENE, HABITS, AND PRACTICES

Personal hygiene practices in the laboratory are directed, in most part, toward the prevention of occupationally acquired physical injury or disease. To a lesser extent, they can raise the quality of the laboratory work by reducing the possibilities for contamination of experimental material. The reasons for many of the recommended precautions and practices are obvious, but, in some instances, amplification will permit a better review of the applicability to any one specific laboratory.

Consequently, what might be forbidden in one laboratory might be only discouraged in another, and be permissible in a third. Nevertheless, adherence to safe practices that become habitual, rather than seasonal or accidental, provides a margin of safety in situations where the hazard is unrecognized. The history of hospital infections illustrates the consequences of人才 unrecognized until too late. The following guidelines, recommendations, and comments are presented with this in mind.

1. Food, candy, gum, and beverages for human consumption will be stored and consumed only outside the laboratory (5,10,26).

2. Foot-operated drinking fountains should be the sole source of water for drinking by human occupants of the laboratory (27).

3. Smoking is not permitted in the laboratory or animal quarters. Cigarettes, pipes, and chewing tobacco will be kept only in clean areas (5,10,29).

4. Shaving and brushing of teeth are not permitted in the laboratory. Ramus, toothbrushes, toothpaste, and cosmetics are permitted only in clean change rooms or other clean areas, and should never be used until after shaving or thorough washing of the face and hands (57).

5. A beard may be undesirable in the labo-

ratory in the case of personnel who deal with aerosolized or airborne contamination, because it retains particulate contamination more persistently than clean-shaven face, and before smoking. The provision of handashing facilities should be the sole source of water for drinking by human occupants of the laboratory (27).

6. Personal items, such as coats, hats, arm bands or leg bands, umbrellas, purses, etc., do not belong in the laboratory. These articles should be kept elsewhere (29).

7. Plants, cut flowers, an aquarium, rats, and mice or other rodent housing facilities should be confined to the institutional library should be used only in the clean areas as much as possible (10,27).

8. When change rooms with showers are provided, the employee should furnish skin lotions (27).

9. When employees are subject to poten-

tial occupational infection, the shower and/ or face/hand-washing facilities should be provided with germicidal soap (8,27).

10. Personal cloth handkerchiefs should also be used in the laboratory when feasible. Cleansing tis-

sues should be available instead.

11. Hand washing for personal protection: (i) This should be done promptly after removing protective gowns. Tests show it is not unusual for microbial or chemical contamination to be present despite use of gloves; due to unrecognized small holes, abrasions, tears, or cuts in the wrist.

(ii) Throughout the day, at intervals dictated by the nature of the work, the hands should be washed. Presence of a wrist watch discourages adequate washing of the wrist (10,23).

(iii) Hands should be washed after re-

moving the protective cloth, before leaving the laboratory area, before eating, and before smoking. The provision of hand cream by the employee encourages these prac-

tices (8,10).

(iv) A disinfected wash or dip may be desirable in some cases, but its use must not be carried to the point of causing roughening, discoloration or sensitization of the skin.

12. Footwear. In moderate and high contamination areas, rubber overshoes or storm rubber or overshoes, umbrellas, or heavy walled glass flasks or other protective clothing. Masks are also worn to provide full protec-

tion. The capillary space between the cor-

nea and the lens is a reservoir of bacteria and fungi that can lodge these organisms in the anterior chamber of the eye. Caustic chemicals trapped in this space can cause chemical conjunctivitis, keratitis, and perforation of the cornea and can result in a cataract.

13. Masking. Masking is another type of respiratory protection designed to prevent self-inoculation of personnel and the escape of droplets from the nose or mouth (9). A half-mask respirator or ventilated hood will suffice. A half- mask respirator does not protect the eyes, which are an avenue of infection to humans through the conjunctiva and the nose.

14. When employees are subject to poten-

tial contamination of experimental mate-

rials, a face mask or respirator should be worn. Respiratory protection is especially important when the employee is being vaccinated for smallpox, since two weeks' absence may be required for returning to work with normal cell cultures or with susceptible animals, especially the normal mouse colony (23).

15. In the event that approval is still in doubt, the author's paper is of little value for personal respiratory protection (29). It is designed to prevent escape of droplets from the nose or mouth (33C). If bioaerosol respirators do not provide respiratory protection, then nothing but a full face res-

pirator or ventilated hood will suffice. A half-

mask respirator does not protect the eyes, which are an unvalued avenue of Infection through the conjunctiva and the nose.

16. Exposure of personnel to potentially hazardous materials has resulted in the presumption that a high percentage of laboratory personnel are vaccinated for smallpox. The infection rate of smallpox has been reported as 15.4/100,000 persons (23).

17. The purpose of this summary is to alert laboratory personnel to the existence of this source of contamination (9).

18. Fungal vaccinated for smallpox may be carriers of vaccinia virus during the phase before the smallpox pustules appear and may require permission of the appropriate super-

visor, because two weeks' absence may be required for returning to work with normal cell cultures or with susceptible animals, especially the normal mouse colony (23).

19. Fibrous materials are important, laboratory-only shoes can reduce the microbial load brought into the

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laboratory each day by street shoes. Shoes are efficient transporters. In one study, there were 4 to 850 times as many bacteria per square centimeter on the laboratory footwear as on the floor itself (30).

V. CARE AND USE OF LABORATORY ANIMALS (10, 32-37)

A. Care and handling. 1. Special attention must be given to the humane treatment of all laboratory animals. The National Academy of Sciences has recommended the Animal Welfare Act of 1970. The implementing rules and regulations appear in the Code of Federal Regulations (CFR) Title 9, Chapter 1. Under Parts 1, 2, 3, and 4, recommended provisions and practices that meet the requirements of the Act have been published by the U.S. Public Health Service (33).

2. There are specific minimum requirements (33) concerning the caging, feeding, watering, and sanitation for dogs, cats, guinea pigs, hamsters, rabbits, and nonhuman primates. To meet these requirements, the animal room supervisor must have a copy of 9 CFR Chapter 1, Subchapter A, Parts 1, 2, 3, 4.

3. Each laboratory should establish procedures to ensure the use of animals that are free of diseases prejudicial to the proposed experiments and free from carriers of disease or vectors. Care should be taken to avoid danger other experimental animals or personnel (10).

4. Cages containing infected animals (10).

1. Careful handling procedures should be employed to minimize the dissemination of disease to experimental animals.

2. Cages should be sterilized by autoclaving. Refuse, bowls and watering devices should remain in the cage during sterilization.

3. All watering devices should be of the "non-drip" type.

4. Cages should be examined each morning and at each feeding time so that dead animals can be removed.

5. Heavy gloves should be worn when feeding, watering, handling, or removing infected animals. Bare hands should never be placed in the cage to move any object therein.

6. When animals are to be injected with biohazardous material, the animal caretaker should wear protective gloves and the laboratory workers should wear surgical gloves. Animals should be properly restrained to avoid severe injury that results in the injection of biohazard material, as well as to prevent injury to the animal and to personnel.

7. Animals exposed to biohazardous aerosols should be housed in ventilated cages, in gas-tight enclosures in animal rooms designed for protection of personnel by use of ventilated suit.

8. Animals inoculated by means other than by aerosol should be housed in equipment suitable for the level of risk involved.

9. Infected animals to be transferred between buildings should be placed in ventilated cages or other aerosol-proof containers.

10. The overbite canine teeth of large monkeys present a particular problem. Infected with this disease, and persons in close contact with such animals may become infected. After the overbite occurs in this country, chimpanzees apparently no longer transmit the disease. A record should be maintained for each newly imported animal. A sign should be posted at rooms housing these animals to warn that the animals are potentially infectious.

D. General Guidelines that Apply to Animal Room Maintenance (10).

1. Doors to animal rooms should be kept closed at all times except during feeding and care.

2. Unauthorized persons should not be permitted to enter animal rooms.

3. A cot should be kept in each animal room for disinfecting gloves and hand, for general decontamination. When such animals are present. Hands, floors, walls, and cage racks should be washed with an approved disinfectant at the recommended strength as frequently as the supervisor directs.

4. Floor drains in animal rooms, as well as floor drains throughout the building should be flooded with water or disinf ectant periodically to prevent backup of sewer gasses.

5. Shootings or other refuse on floor should not be washed down the floor drain because such refuse clogs the sewer lines.

6. An Infect and rodent control program should be maintained in all animal rooms and in animal food storage areas.

7. Special care should be taken to prevent live animals, especially mice, from finding their way into disposable trash.

D. Necropy of infected animals (10).

1. Necropy of infected animals should be carried out by trained personnel in Biological Safety Cabinets with the hinged glass doors removed. Work should be performed with or without attached gloves, and a respirator should be used at the discretion of the supervisor.

2. Surgeons gowns should be worn over laboratory clothing during necropsy.

3. Rubber gloves should be worn when performing necropsies.

4. The fur of the animal should be wetted with a suitable disinfectant.

5. Small animals should be pinned down or fastened on wood or metal in a metal tray.

6. Upon completion of necropsy, all potentially biohazardous material should be placed in suitable containers and sterilized immediately.

7. Contaminated instruments should be placed in a horizontal bath containing a suitable disinfectant.

8. The inside of the Biological Safety Cabinets and other potentially contaminated surfaces should be disinfected with a suitable germicide.

9. Grossly contaminated rubber gloves should be cleansed, disinfected before removal from the hands, properly disposed of, and sterilized.

10. Dead animals should be placed in proper leak-proof containers,autoclaved and properly tagged before being placed outside for removal and incineration.

VI. DECONTAMINATION AND DISPOSAL

A. Introduction. Available data on the efficacy of various decontaminants for etiological agents indicate that no major surprises remain regarding susceptibility of organisms containing recombinant DNA molecules. In the absence of adequate information, tests to determine the efficacy of candidate decontaminants should be conducted with the specific agent of interest. The goal of decontamination is not only the protection of personnel and the environment from exposure to infectious agents, but also the natural contamination of experimental materials by a variable, persistent, and unwanted background of microorganisms. The principal factor should be considered in selecting decontamination materials and methods.

B. Decontamination Methods. Physical and chemical means of decontamination are generally limited to four main categories: Heat; liquid decontaminants; Vapors and Gases; and UV Radiation.

1. Heat. The application of heat, either moist or dry, is recommended as the most effective method of decontamination. Moist heat at 131 °C under pressure in the autoclave is the most convenient method of rapidly achieving a sterilizing effect.

2. Liquid Decontaminants. In general, the liquid decontaminants find their most practical use in surface decontamination and, at sufficient concentration, as decontaminants of liquid wastes for final disposal in sanitary sewer systems. There are many misconceptions concerning the use of liquid decontaminants. This is due largely to a characteristic capacity of such liquids to perform graphically in the test tube and to fail miserably in a practical situation. Such failures often occur because the liquid was not given to such factors as temperature, time of contact, pH, concentration, and the presence or state of inanimate and organic material at the site of application. Small variations in the above factors may make liquid decontaminants ineffective or live. For this reason, even when used under highly favorable conditions, complete reliability should not be placed on liquid decontaminants when the end result must be sterility.

3. Vapor and Gases. A variety of vapors and gases possess decontamination properties. The most useful of these are formaldehyde and ethylene oxide. When these can be employed, they are particularly useful in the control of conditions of temperature and humidity, excellent decontamination can result.

Vapor and gas decontaminants are primarily useful in decontaminating: (i) Biological Safety Cabinets and associated efficient air-handling systems and air filters; (ii) bulky or stationary equipment; (iii) liquid surface decontaminants; (iv) complete rooms; and (v) buildings and associated air-handling systems.

4. Radiation. The usefulness of ultraviolet (UV) irradiation as a decontaminant is limited by its low penetrating power. No information is available concerning the effectiveness of UV irradiation for decontaminating microorganisms containing recombinant DNA molecules. Most of the work that has been done has been based on the results of experiments limiting particular anticipated environmental conditions. The effect of UV of sufficient light is generally of limited application and is primarily useful in air locks and animal holding areas for controlling low levels of airborne contaminants.

No one procedure or material will solve all decontamination problems. The only method of achieving the efficacy desired by technology is to critically examine the results.
The occurrence of a laboratory spill is the decontamination of an overt biological spill. The occurrence of a spill is minimal if it occurs in a Biological Safety Cabinet provided spattering to the outside of the cabinet does not occur. The effectiveness of containment of a decontaminant and a thorough wipe down of the interior surfaces of such cabinets will usually be effective for most materials. But, some solid but gaseous decontaminants would be required to rid the interior sections of the cabinet of contaminants. Each researcher must realize that in the event of an overt accident, research materials such as tissue culture, media, and animals within such cabinets may well be lost to the experiment.

The greater problem arises if the incident occurs in the open laboratory. All laboratory protocols should be designed to prevent such occurrences. The first action in the event of an overt laboratory spill is evacuation of the affected area to minimize the exposure of personnel involved. Next, the spill area should be isolated to prevent exposure of personnel and experimentation to experimental and research materials initially entering the laboratory area. The procedures adopted must be rapidly effective for both solid and liquid, either by manual or mechanical means. Disposable (6) Resealable film packages (7) for transport of animals, and large carcasses or tanks of fluids which can be left outside and drawn from as required. Reduction of personnel in the facility will free autoclaves and other decontamination and disposal processes within the laboratory for more rapid and efficient handling of materials known to be contaminated.

Inevitably, disposal of materials raises the question, "How can we be sure that the materials have been treated adequately to ensure their disposal does not constitute a hazard?" In the laboratory, the problem is often solved by requiring that each investigator decontaminate all contaminated materials not of immediate use at the end of each day. The use of disposable containers for routine disposal. In larger laboratories where the mass of materials for disposal and medical waste is large, the use of autoclaves as a decontamination procedure will be found in the actual research. In either situation, a case can be made for establishing a positive control, or a set of materials to be disposed of. This may consist of a tagging system stating that the materials are either sterile or contaminated.

Disposal of spills in the laboratory and animal holding areas will be required for research projects ranging in size from an individual researcher to those involving large numbers of researchers of many disciplines. Procedures and facilities to accomplish this will range from the simplest to the most elaborate. The primary consideration in any of these is to dispel the notion that laboratory wastes can be disposed of in the same manner and with as little thought as house- hold wastes. Selection and enforcement of safe procedures for disposal of laboratory materials are of no less importance than the actual research for the accomplishment of research objectives.

Materials of dissimilar nature will be common in laboratories studying recombinant DNA molecules. Examples are combinations of these organisms, radioactive isotopes, and concentrated viruses or nucleic acids. These may require isolation techniques and guidelines in arriving at the most practical approach for their decontamination.

Characteristics of chemical decontaminants in common use in laboratory operations. Every person actively working with recombinant DNA molecules, no matter how remote the field of specialization, will, from time to time, find himself dealing with these materials, equipment, and specialized instruments. Chemical decontamination is necessary because, until now, the most rapid and reliable method of sterilization is not normally feasible for decontaminating large spaces, surfaces, and stationary equipment. Moreover, high temperatures and moisture often damage delicate instruments, particularly those having complex optical and electronic features. Materials with chemical characteristics are, for the most part, available as powders, liquids, crystals, and gels. These materials should be added to tap water for application as surface decontaminants, and some, when added in sufficient quantities, find use in decontamination of bulk liquids. Chemical decontaminants that are gaseous at room temperatures are useful as space-penetrating decontaminants to decontaminate areas at reasonably elevated temperatures and can act as either aqueous surface or gaseous space-penetrating decontaminants.

Inactivation of microorganisms by chemical decontaminants may occur in one or more of the following three ways: (1) Coagulation and denaturation of protein, (2) Binding to enzymes, or inactivation of an essential enzyme by a chemical, and (3) Formation, binding, or destruction of enzyme-substrate complex. The relative resistance to the action of chemical decontaminants can be substantially altered by such factors as: Concentration of active ingredient, duration of contact, pH, temperature, humidity, and presence of extraneous organic matter. Depending upon how these factors are manipulated, the degree of success achieved with chemical decontaminants may range from minimal inactivation of target microorganisms to an indicated sterilization within the limits of sensitivity of the various systems employed.

There are dozens of contaminants available under a wide variety of trade names. In general, these decontaminants can be classified as halogens, acids or alkalines, heavy metal salts, quaternary ammonium compounds, phenolic compounds, organic solvents, amines. Unfortunately, the more active the decontaminant the more likely it will possess a number of undesirable characteristics. For example, peracetic acid is a fast-acting, universal decontaminant. However, in the concentrated state, it is a hazardous compound that can readily decompose with explosive violence. When diluted for use, it has a pungent, irritating odor, and is extremely corrosive to metals. Nevertheless, it is such an outstanding decontaminant that it is commonly used in germ-free animal studies despite these undesirable characteristics.

The halogens are probably the second most active group of decontaminants. Chlorine, iodine, bromine, and fluorine will rapidly kill bacterial spores, viruses, rickettsiae, and fungi. These decontaminants are effective over a wide range of temperatures. In fact, chlorine has been shown to be effective at -190°C. (On the other hand, phenols and formaldehyde have high temperature coefficients.) The halogens have several undesirable features. For example, sodium hypochlorite reacts with p- toluenesulfonic acid to form chloramines, and iodide ions react with certain surface-active agents to form the popular Iodophors. These "amended" halogens are pungent, odorless, and relatively noncorrosive to metals. However, the halogens are highly reactive with metallic and, because they are reactive, they are good germicides. When a halogen acts as a decontaminant, free halogen is the effective agent. However, the halogenating agent, the halogen, with other compounds to decrease the corrosive effect will also decrease the germicidal power. A trade-off exists.

Ineffectiveness of a decontaminant is due primarily to the failure of the decontaminant to contact the microorganism rather than failure of the decontaminant to act. If one places an Item in
a liquid decontaminant, one can see that the item is covered with tiny bubbles. Of course, the area under the bubbles is dry, and microorganisms in these dry areas will not be affected by the decontaminant. Scrubbing an item with a dry, noncorrosive to metal, active and effective, and inexpensive. 6. Chlorine. This halogen is a universal disinfecting agent, particularly effective against all microorganisms, including bacterial spores. Chlorine combines with protein and rapidly decreases in concentration. Aqueous, available chlorine is an active element. It is a strong oxidizing agent, corrosive to metals, and it is more effective under alkaline than under acid conditions. Its effectiveness lies in the fact that fresh solutions must be prepared frequently. Sodium hypochlorite is not completely inactivated by solutions of the decontaminants. An excellent decontaminant can be prepared from household or laundry bleach. These bleaches usually contain 5.25 ppm of available chlorine, and, although a nonionic detergent such as Naccon is added in a concentration of about 0.7 percent, a very good decontamination is created. 7. Formaldehyde. The characteristics of chlorines and iodines are similar. One of the most popular groups of decontaminants used in the laboratory is formaldehyde. The use of formaldehyde vapor or gas to inactivate microorganisms is widespread use, as a gaseous solution, a vapor, or a gas reasonably be expected to contact the microorganisms, and can effectively destroy all of the decontaminants. The solution will be easily lost if the concentration of the decontaminant is low in the test tube. Similarly, the use of formaldehyde to sterilize or decontaminate areas is based on the assumption that the target microorganism is present in the test tube. The use of formaldehyde vapor or gas has already been discussed. Other chemical decontaminants which have been used in this way include ethylene oxide, paraffin, formaldehyde, and ethylene oxide. When these can be used in closed systems and under controlled conditions of temperature and humidity, decontamination can be obtained. Residues from ethylene oxide must be removed by aeration; otherwise, it is convenient to use, versatile, and noncorrosive. Paraffin is corrosive to metals and rubber. BPL in the form of sodium thiosulfate, tetracetate, and virus. It has a half-life of 3.5 hours when mixed with water, is easily neutralized with water, and lends itself to removal by aeration. The National Institutes of Health does not recommend BPL as a decontaminant because it has been identified as a suscep- tible factor in the treatment of patients. H. Residual action of decontaminants. As noted in the preceding discussion of decon- tamination and sterilization, when chemical decontaminants are used, it is considered desirable to achieve a level of microorganisms that is below the threshold of detectability. A decontaminant selected on the basis of its effectiveness against microorganisms on any range of the resistance scale will be ef- fective in the control of biological contamination.
effective against microorganisms lower on the scale. Therefore, if decontaminants that effectively control spore forms are selected for routine laboratory decontamination, it can be assumed that any other microorganisms generated by laboratory operations, even in high concentrations, would also be inactivated.

An additional area that must be considered and for which there is little definitive information available is "inactivation" of nucleic acids. Nucleic acids often have better survival characteristics under adverse conditions than do the intact virions and cells from which they were derived. Strong oxidizers, strong acids and bases, and either practical or experimental concentrations of RNA, DNA, RNA overdue with nucleic acids. Their ability to destroy the nucleic acid being studied, however, should be confirmed by the experimenter's laboratory. Because of innate differences in the chemistry of RNA and DNA the effectiveness of a decontaminant for one cannot be extrapolated to the other. For example, RNA molecules are susceptible to mild alkaline hydrolysis by virtue of the free hydroxyl group in the 2' position, whereas DNA molecules are not susceptible to mild alkaline hydrolysis.

The following checklist outlines a portion of the items requiring critical review by the laboratory supervisor. It is not intended to be complete but is presented as an example of the detailed manner in which housekeeping in the biological laboratory complex must be viewed.

**VII. HOUSEKEEPING**

A. **Introduction.** Well-defined housekeeping procedures and schedules are essential in reducing the risks of working with etiological agents and in protecting the integrity of the research program. This is particularly true in the biological laboratory operating under less than total containment concepts and in all areas related to the housing of animals, whether or not they have been intentionally infected. A well-conceived and well-executed housekeeping program limits physical clutter that could distract the attention and interfere with the activities of laboratory personnel at a critical moment in a potentially hazardous procedure, provides a work area that will not in itself be a source of physical injury or contamination, and provides an area that promotes the effective use of decontaminants in the event of the inadvertent release of a harmful agent. Least immediately evident are the benefits of establishing, among personnel of widely varying levels of education, an appreciation of the nature and sources of biological contamination.

Housekeeping is an ominous term that can be interpreted as broadly or as narrowly as one chooses. It can be seen that many of the procedures found under special headings, such as decontamination, disposal, and animal care, are, in reality, specific instructions for safely accomplishing otherwise routine housekeeping chores. In these safety precautions for research on recombinant DNA molecules, it has been elected to address specifically only those of a juridical nature under the subject of housekeeping.

The objectives of housekeeping in the biological laboratory are to:

1. Provide an orderly work area conducive to the accomplishment of the research program.
2. Provide work areas devoid of physical hazards.
3. Provide a clean work area with background contamination ideally held to a zero level but more realistically to a level such that extraordinary measures in sterile techniques are not required to maintain integrity of the biological systems being researched.
4. Prevent the accumulation of materials from current and past experiments that constitute a hazard to laboratory personnel.
5. Prevent the creation of aerosols of hazardous materials as a result of the housekeeping procedures.

Procedures developed in the area of housekeeping should be based on the highest level of risk to which the personnel and integrity of the experiments will be subject. Such an approach avoids the confusion of multiple practices and retraining of personnel. The primary function, then, of routine housekeeping procedures is to prevent the accumulation of organic debris that (i) may harbor microorganisms that are a potential threat to the integrity of the biological systems under investigation, (ii) may enhance the survival of microorganisms inadvertently released in experimental procedures, (iii) may retard penetration of decontaminants, (iv) may be transferable from one area to another on clothing and shoes, (v) may with sufficient buildup, become a biohazard as a consequence of secondary aerosolization by personnel and air movement, and (vi) may cause allergen-sensitization of personnel, e.g., animal danders.

Housekeeping in animal care units has the same primary function as that stated for the laboratory and should, in addition, be as meticulously carried out in quarantine and conditioning areas as in areas used to house experimentally infected animals. No other areas in the laboratory have the constant potential for creation of significant quantities of contaminated organic debris than do animal care facilities.
Supply - Storage

- particulate air.
- particulate matter and a follow-up wet floor squeegee.
- cleaned and availability of floor drains, re-
- ning or vacuum cleaning with a nonspecific environmental aerosols. Wet mop-
- known.
- edgeable of its particular requirements, 
- supervisor must determine the frequency with 
- and on a cooperative baslW for areas
- homekeeping is the assignment 
- who are knowledgeable 
- UV
- al to a convenient 1oo0r drain
- sign and.quality in the selection 
- the
- Others
- Waste Water Disposal
- Waste Accumulations
- Vacuum Cleaners
- Mops
- Instruments
- Incubators
- Glassware
- Equipment Storage
- Cleaning Solution Disposal
- Ceilings
- Bench Tops and Other Work Surfaces
- Animal Bedding Storage
- Aisles
- Floors

After cleaning up

- B. Housekeeping in the laborato
- moped pickup with a wet vacuum that 
- moped, pickup with a wet vacuum that 
- llls effect may pump dust out of the bag 
- that collect the major debris in a tank and 
- by use of 
- in large
- Dry material vacuum-collected during these 
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- of sporulation of dust should 
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Wet mopping—two-bucket method. Wet mopping of floors in laboratory and animal care areas is, from a safety standpoint, most conveniently accomplished using a two-bucket system. The principal feature of such a system is that fresh detergent-decontaminant solution is always applied to the floor from one bucket, while all spent cleaning solution is wrung from the mop into a second bucket. Compact, dolly-mounted double-bucket units with foot-operated wringers are available from dolly-mounted double-bucket units with foot-operated wringers are available from foot-operated wringers are available from dolly-mounted double-bucket units with foot-operated wringers are available from dolly-mounted double-bucket units with foot-operated wringers are available from dolly-mounted double-bucket units with foot-operated wringers are available from dolly-mounted double-bucket units with foot-operated wringers are available from dolly-mounted double-bucket units with foot-operated wringers are available from

VIII. CLEAN-UP OF BIOHAZARDOUS SPILLS

A. Biohazardous spill in a biological safety cabinet. Chemical decontamination procedures should be initiated at once while the majority of the work force has dispersed, to prevent escape of contaminants from the cabinet. 1. Spray or wipe walls, work surfaces, and equipment. Rinse is an iodophor-decontaminant (Wescodyne or equivalent). A decontaminant detergent has this advantage. Important because extraneous organic substances frequently interfere with the reaction between the iodophor and the active agent of the decontaminant. Operator should wear gloves during this procedure. 2. Flood the top work surface tray, and, if a Class II cabinet, drain and catch bowls below the work surface, with a decontaminant and allow to stand 10–15 minutes. 3. Remove decontaminant from the tray by wiping with a sponge or cloth soaked in a decontaminant. For Class II cabinets, lift out tray and removable grates. For Class I cabinets, replace in position and drain decontaminant from cabinet base into an autoclavable bag and autoclave. 4. Biohazardous spill outside a biological safety cabinet. a. Hold your breath, leave the room immediately, and close the door. b. Warn others not to enter the contaminated area. c. Remove and put into a container contaminated garments for autoclaving and thoroughly wash hands and face. d. Wait 30 minutes to allow dissipation of aerosols created by the spill. e. Put on a long-sleeve gown, mask, and rubber gloves before reentering the room. f. Using an autoclavable dust pan and squeegee, transfer all contaminated materials (paper towels, glass, liquid, gloves, etc.) into a deep autoclave pan. Cover the pan with aluminum foil or other suitable cover and autoclave according to standard directions. g. Further radioactive survey should be made of the spill area, dust pan, and squeegee, and with a Geiger counter, or a smoke should be taken and counted in a liquid scintillation counter.

B. Radioactive biohazard spill outside a biological safety cabinet. In the event that a biohazardous spill also involves a radiation hazard, the clean-up procedure may have to be modified, depending on an evaluation of the relative degree of relative biological and radiological hazard. 1. Spray or wipe walls, work surfaces, and equipment. 2. Flood the top work surface tray, and, if a Class II cabinet, drain and catch bowls below the work surface, with a decontaminant and allow to stand 10–15 minutes. 3. Remove decontaminant from the tray by wiping with a sponge or cloth soaked in a decontaminant. For Class II cabinets, lift out tray and removable grates. For Class I cabinets, replace in position and drain decontaminant from cabinet base into an autoclavable bag and autoclave. 4. Biohazardous spill outside a biological safety cabinet. a. Hold your breath, leave the room immediately, and close the door. b. Warn others not to enter the contaminated area. c. Remove and put into a container contaminated garments for autoclaving and thoroughly wash hands and face. d. Wait 30 minutes to allow dissipation of aerosols created by the spill. e. Put on a long-sleeve gown, mask, and rubber gloves before reentering the room. f. Using an autoclavable dust pan and squeegee, transfer all contaminated materials (paper towels, glass, liquid, gloves, etc.) into a deep autoclave pan. Cover the pan with aluminum foil or other suitable cover and autoclave according to standard directions. g. Further radioactive survey should be made of the spill area, dust pan, and squeegee, and with a Geiger counter, or a smoke should be taken and counted in a liquid scintillation counter.
sulfuric acid will corrode pipes, and contaminants may lose their inactivating ability upon standing. The introduction of a cartridge-type filter that is moisture resistant and has a rated capacity to remove particles 350 nm (0.3μm) or larger in size provides an effective barrier to virus aerosols.

The secondary reservoir and filtration apparatus can be assembled from readily available parts as shown in Figure 1. A length of plastic tubing ¾ inch I.D. x ¾ inch wall is attached at one end of the reservoir and at the other end to the lower arm of a filtration and media storage flask. These flask vary in capacity from 500 to 4000 ml, the choice of flask depending on available space and amount of fluid that could be accidentally aspirated. A second tube of the same dimensions is attached from the upper arm of the flask to the inlet port of the disposable filter assembly. The third tube is attached from the filter assembly to a vacuum source. The tubes are securely held to the filter by fittings supplied with the filter and the other tubing connections can be secured by worm drive hose clamps.

Ideally the flask should be placed higher than the reservoir of collection vessel. If fluid is accidentally drawn into the flask, the liquid can drain back into the reservoir by gravity if the connection at the vacuum line is broken. This prevents the loss of fluid which the investigator needs to retain.

Should the flask be used only for the recovery and storage of waste fluids, then the investigator may use a disposable filter assembly. The third tube is attached from the filter to the lower arm of the flask. A length of plastic tubing 250 ml or greater may be placed outside the secondary container(s). Descriptions of this packaging method are given in Table III.

2. Volumes of 50 ml or Greater. Material shall be placed in a securely closed, watertight container (primary container) which shall be enclosed in a second, watertight container (secondary container). Single primary containers shall not contain more than 500 ml of material. However, two or more primary containers whose combined volumes do not exceed 500 ml may be placed in a single secondary container. The space at the top, bottom, and sides between the primary and secondary containers shall contain sufficient non-particulate absorbent material to absorb the entire contents of the primary container(s) in case of breakage or leakage. Each set of primary and secondary containers shall then be enclosed in an outer shipping container constructed of corrugated fiberboard, cardboard, wood, or other material of equivalent strength.

If dry ice is used as a refrigerant, it must be placed outside the secondary container(s) as described in paragraph (a). Descriptions of this packaging method are given in Table III.

X. PACKAGING AND SHIPPING

A. Introduction. Federal regulations and carrier tariffs have been promulgated to ensure the safe transport of hazardous biological materials. The NIH Guidelines specify that all DNA recombinant materials will be packaged and shipped in containers that meet the requirements of these regulations and carrier tariffs. In addition when any portion of the recombinant DNA material is derived from an etiologic agent listed in paragraph (e) of 42 CFR 72.25 (which is included at the end of this section, page 32-66) the labeling requirements in these regulations and carrier tariffs shall apply.

B. Packaging of recombinant DNA materials. 1. Volumes less than 50 ml. Material shall be placed in a securely closed, watertight container (primary container) which shall be enclosed in a second, watertight container (secondary container). Several primary containers may be enclosed in a single secondary container. However, all the material in primary containers so enclosed does not exceed 50 ml. The space at the top, bottom, and sides between the primary and secondary containers shall contain sufficient non-particulate absorbent material to absorb the entire contents of the primary container(s) in case of breakage or leakage. Each set of primary and secondary containers shall then be enclosed in an outer shipping container constructed of corrugated fiberboard, cardboard, wood, or other material of equivalent strength.

If dry ice is used as a refrigerant, it must be placed outside the secondary container(s) as described in paragraph (a) (5). Descriptions of this packaging method are given in Table III.

2. Volumes of 50 ml or Greater. Material shall be placed in a securely closed, watertight container (primary container) which shall be enclosed in a second, watertight container (secondary container). Single primary containers shall not contain more than 500 ml of material. However, two or more primary containers whose combined volumes do not exceed 500 ml may be placed in a single secondary container. The space at the top, bottom, and sides between the primary and secondary containers shall contain sufficient non-particulate absorbent material to absorb the entire contents of the primary container(s) in case of breakage or leakage. Each set of primary and secondary containers shall then be enclosed in an outer shipping container constructed of corrugated fiberboard, cardboard, wood, or other material of equivalent strength. A shock absorbent material, in volume at least equal to that of the enclosed materials, shall be placed on the bottom, sides, and top of the secondary container(s). In addition to the address label, the label for Etiologic Agents/Biomedical Material shall be affixed to the outer shipping container. This label is described in paragraph (e) (4) of 42 CFR 72.25.

3. Materials which contain any portion of an etiologic agent listed in paragraph (e) of 42 CFR 72.25. Material data forms, letters, and other information identifying or describing the material should be placed around the outside of the secondary container. In addition to the address label, the label for Etiologic Agents/Biomedical Material shall be affixed to the outer shipping container. This label is described in paragraph (c).

D. Additional shipping requirements and limitations for recombinant DNA materials—4. Domestic Transportation. Civil Aeronautics Board Rule No. 82 (Air Transport Association Restricted Articles Tariff 6-D) requires that a Shipper's Certificate, described in paragraph 4, be affixed to all shipments which bear the ETIOLOGIC AGENT/BIO MEDICAL MATERIALS label required under the provisions of 42 CFR 72.25(c)(1). The Certificate must be completed in duplicate and affixed to the outer shipping container.

This is to certify that the contents of this container are properly classified, described, packed, marked and labeled and are in proper condition for carriage by air according to all applicable carrier and governmental regulations. For International shipments add "and to the IATA Restricted Articles Regulations". This container is within the limitations prescribed for PASSENGER AIRCRAFT CARGO ONLY (cross out nonapplicable).
Shipments of recombinant DNA Materials exceeding 50 ml in volume and containing any portion of an etiologic agent listed in paragraph (c) of 42 CFR 72.25 are restricted, by DOT regulations, to transport by cargo only aircraft. When the volume of a single primary container exceeds the 50 ml limitation, this restriction must be indicated on the Shipper’s Certificate by crossing out “Passenger Aircraft.”

When dry ice is used as a refrigerant an “ORAA—Group A—DRY ICE LABEL” should be affixed to the outer shipping container.

The amount of dry ice used and the date packed should be designated on the label.

1. International Transportation.—In addition to the packaging and labeling requirements of the regulations previously cited, international shipments of recombinant DNA materials in which any portion of the material is derived from an etiologic agent listed in paragraph (c) of 42 CFR 72.25 must have one or more of the following documents—depending on the country of destination:

   (1) Parcel Post Customs Declaration (PS 2966) tag.
   (2) Parcel Post Customs Declaration (PS 2966-A) label.
   (3) International Parcel Post—Instructions Given by Sender (POD 2022) tag.
   (4) Dispatch note (POD 2072) tag.
   (5) “Violet Label”
   (6) Shipper’s Certificate specified in the current International Air Transport Association Tariff. Individual country requirements are listed in “International Postage Rates and Fees” (USPS Publication 61).

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TABLE III

<table>
<thead>
<tr>
<th>Volume (ml)</th>
<th>Primary Container</th>
<th>Packing</th>
<th>Secondary Container</th>
<th>Packing</th>
<th>Outer Shipping</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>Sealed vial(s) or small glass test tube, screw cap or stopper, taped</td>
<td>s/</td>
<td>Metal can 1&quot; diam. x 7&quot; O.D. screw cap</td>
<td>None</td>
<td>Fiberboard metal screw cap, top and bottom; 1-1/2&quot; diam. x 7 to 7-1/2&quot; O.D.</td>
</tr>
<tr>
<td>50</td>
<td>One 20 x 150 mm test tube, screw cap or multiple small vials 3/8&quot; diam.</td>
<td>s/</td>
<td>Metal can 2-1/2&quot; diam. x 6-1/2&quot; high O.D. screw cap</td>
<td>None</td>
<td>Fiberboard metal screw cap, top and bottom; 3-1/4&quot; diam. x 7 to 7-1/2&quot; O.D.</td>
</tr>
<tr>
<td>50</td>
<td>Plastic screw-cap bottle or Pyrex glass with rubber stopper</td>
<td>s/</td>
<td>Metal can 2-1/2&quot; diam. x 6-1/2&quot; high O.D. screw cap</td>
<td>None</td>
<td>Fiberboard metal screw cap, top and bottom; 3-1/4&quot; diam. x 7 to 7-1/2&quot; O.D.</td>
</tr>
<tr>
<td>50</td>
<td>Multiple watertight vials or tubes, taped stoppers</td>
<td>s/</td>
<td>One or more friction-seal tin-cans 306 x 400 or larger</td>
<td>s/</td>
<td>Fiberboard box</td>
</tr>
</tbody>
</table>

*The flexibility of the plastic bottle requires that a stopper or screw cap be secured In place by adhesive tape. The usual equivalent-size glass flat-sided prescription bottle is too fragile for use. For air transport, all stoppers, corks, and caps on primary containers must be secured In place with wire, tape, or other means, and all screw-capped containers of unfrozen liquid must be placed In 5 or 6 polyvinyl tubing heat-sealed at both ends to prevent atmospheric decompression that may result in leakage past the screw cap.

O.D. = outside dimensions.

s/ Nonparticulate absorbent material at top, bottom and sides that will completely absorb contents of the primary container(s).

3/ 610 x 708 and 804 x 908 are trade designations for outside dimensions of 6-10/16 inches diameter x 7-8/16" height, and 8-4/16" x 9-8/16".

f/ None required, but with the 306 x 400 cans or larger cans use sufficient nonparticulate shock-absorbent material to prevent rattling.

If materials are to be refrigerated, it is recommended that an overpack be used to contain the refrigerant and the secured (original) outer shipping container. A leak proof outer container must be used for water ice. If dry ice is used the outer container must permit release of carbon dioxide. Interior supports must be provided to hold the container(s) in the original position(s) after wet or dry ice has dissipated.
### Table IV

**Description of Packages for Material in Volumes of 10 ml or Greater**

<table>
<thead>
<tr>
<th>Volume (ml)</th>
<th>Primary Container</th>
<th>Secondary Container</th>
<th>Packing With or Without Reference</th>
<th>Outer Shipping Container</th>
<th>With or Without Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 100 ml</td>
<td>Plastic or Pyrex glass screw cap bottle, rubber or white rubber stopper, taped</td>
<td>500 ml plastic bottle or Pyrex glass, taped</td>
<td>S10, screw seal tin can, 400 x 700, top soldered or clipped at 4 points</td>
<td>Fiberboard box closely fitting the styrofoam box, taped shut</td>
<td>Corrugated fiberboard or cardboard box, taped shut</td>
</tr>
<tr>
<td>100 ml max.</td>
<td>Oke 100 ml plastic bottle or Pyrex glass, taped</td>
<td>No. 3 crep seal tin can, 400 x 700, top soldered or clipped at 4 points</td>
<td>Fiberboard box closely fitting the styrofoam box, taped shut</td>
<td>VIC cardboard box P3 type, 9-3/16 x 9-3/16 high O.D. taped shut with 3&quot; type P33 tape</td>
<td></td>
</tr>
<tr>
<td>200 ml max.</td>
<td>Two 100 ml plastic bottle or Pyrex glass, taped</td>
<td>No. 3 crep seal tin can, 404 x 804, top soldered or clipped at 4 points</td>
<td>Fiberboard box closely fitting the styrofoam box, taped shut</td>
<td>VIC cardboard box P3 type, 9-3/16 x 9-3/16 high O.D. taped shut with 3&quot; type P33 tape</td>
<td></td>
</tr>
<tr>
<td>250 ml max.</td>
<td>One 250 ml plastic bottle or Pyrex glass skirted rubber stopper, taped</td>
<td>No. 3 crep seal tin can, 404 x 804, top soldered or clipped at 4 points</td>
<td>Fiberboard box closely fitting the styrofoam box, taped shut</td>
<td>VIC cardboard box P3 type, 9-3/16 x 9-3/16 high O.D. taped shut with 3&quot; type P33 tape</td>
<td></td>
</tr>
<tr>
<td>500 ml max.</td>
<td>Two 250 ml plastic bottle or Pyrex glass bottles, taped</td>
<td>Two-gallon friction-seal tin can, 600 x 1000, top soldered or clipped at 4 points</td>
<td>Fiberboard box closely fitting the styrofoam box, taped shut</td>
<td>VIC cardboard box P3 type, 12-1/4 x 12-1/4 high O.D. taped shut with 3&quot; wide P33 tape</td>
<td></td>
</tr>
<tr>
<td>500 ml max.</td>
<td>500 ml Pyrex glass bottle, rubber skirt, screw cap bottle, taped, or 500 ml plastic bottle, narrow or wide mouth, screw cap taped</td>
<td>No. 12 crep seal tin can, 600 x 1000, 2-gallon friction-seal tin can, 604 x 928, top soldered or clipped at 4 points</td>
<td>Fiberboard box closely fitting the styrofoam box, taped shut</td>
<td>VIC cardboard box P3 type, 12-1/4 x 12-1/4 high O.D. taped shut with 3&quot; wide P33 tape</td>
<td></td>
</tr>
</tbody>
</table>

### Notes

- The flexibility of the plastic bottle requires that a stopper or screw cap be secured in place by adhesive tape. The usual equivalent-size plastic flat-sided prescription bottle is too fragile for use. For air transport, all stoppers, corks, and caps on primary containers must be secured in place with wires, tapes, or other means, and all screw-capped containers of unfrozen liquid must be placed in 3 or 6 all polyvinyl chloride heat-sealed at both ends to prevent atmospheric decompression that may result in leakage past the screw cap.
- O.D. = outside dimensions.
- a/ Nonparticulate absorbent material at top, bottom and sides that will completely absorb contents of the primary container(s).
- b/ 610 x 708 and 604 x 928 are trade designations for outside dimensions of 6-10/16 inches diameter x 7-3/16" height, and 4-11/16" x 9-3/16".
- c/ Shock-absorbent material, in volume at least equal to that between the primary and secondary container(s), at the top, bottom, and sides between the secondary container and the outer shipping container. The shock absorbent material shall be so placed that the secondary container(s) does not become loose inside the outer shipping container as the water ice or dry ice is dissipated.
APPENDIX D, Page D-85

ATTACHMENT I

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
ATLANTA, GEORGIA 30333
Telephone: (404) 632-3311, Ext. 3683

TITLE 42—PUBLIC HEALTH

Chapter I—Public Health Service, Department of Health, Education, and Welfare

SUBCHAPTER F—QUARANTINE, INSPECTION, LICENSING

PART 72—INTERSTATE QUARANTINE

Subpart C—Shipment of Certain Things

Section 72.25 of Part 72, Title 42, Code of Federal Regulations, is amended to read as follows:

§ 72.25 Etologic agents.

(a) Definitions. As used in this section:

(1) An "etologic agent" means a viable microorganism or its toxin which causes, or may cause, human disease.

(2) A "diagnostic specimen" means any human or animal material including, but not limited to, excreta, secreta, blood and its components, tissues, and tissue fluids being shipped for purposes of diagnosis.

(3) A "biological product" means a biological product prepared and manufactured in accordance with the provisions of subpart C of part 73, 21 CFR, and (b) of this section, and liquid or solid material, in addition to which is packaged and shipped in accordance with the requirements specified in subparagraphs (1) through (6) of this paragraph:

- Bacterial Agents

  Actinobacillus—spp.

  Arizona hinhawae—spp.

  Bacillus anthracis

  Bartonella—spp.

  Bordetella—spp.

  Borrelia recurrentis, B. denticuli

  Brucella—spp.

  Gluconobacter rapheum, Cl. choanella, Cl. hae-
  moliticum, Cl. histolyticum, Cl. septicum, Cl. septi-
  cum, Cl. tetani.

- Corynebacterium diphtheriae, C. equi, C. hae-
  moliticum, C. pseudotuberculosis, C. pyo-
  genes, C. renale.

- Diplococcus (Streptococcus) pneumoniae, En-
  phyloplces albus.

- Escherichia coli, all enteropathogenic sre-
  types.

- Francisella (Pasteurella) tularensis.

- Haelmonas dysentery, N. influenzae.

- Herelles vaginale.

- Klebsiella—all species and all serotypes.

- Leptospira intermedia—all serotypes.

- Listeria—all species.

- Mima molyphila.

- Moraxella—all species.

- Mycoplasma—all species.

- Neisseria gonorrhoeae, N. meningitidis.

- Pasteurella—all species.

- Pseudomonas aeruginosa.

- Salmonella—spp.

- Shigella—spp.

- Sphaerothes necrophorus.

- Staphylococcus aureus.

- Streptococcus domestica.

- Streptococcus pyogenes.

- Treponema pallidum, T. pallidum, and T.
  pertenue.

- Vibrio fetus, V. comma, including biotype
  El Tor, and V. paracorteticus.

- Yersinia (Pasteurella) pestis.

- FUNgal AGENTS

- Actinomycetes (including Neocleardia species, Actinomycetes species and Arachnella pposi-
  tica).

- Blastomyces dermatitidis.

- Coccidioides immitis.

- Cryptococcus neoformans.

- Histoplasma capsulatum.

- Paracoccidioides brasiliensis.

- VIIR. RICKETTSIA, AND CHAMPSAAL AGENTS

- Adenoviruses—human—all types.

- Arboviruses.

- Calicivirus.

- Chlamydiae—spp. and 0 viruses—all types.

- Cytomegalovirus.

- Dengue virus.

- Enteroviruses—types.

- Encephalomyocarditis virus.

- Hemorrhagic fever agents, including Critical
  hemorrhagic fever (Congo), Junin, and Machupo viruses, and others as yet undis-
  covered.

- Hepatitis-associated antigen.

- Hepatitis-B virus—members.

- Infectious bronchitis-like virus.

- Influenza viruses—all types.

- Lassa virus.

- Lymphocytic choriomeningitis virus.

- Marburg virus.

- Measles virus.

- Staphylococcal virutes—types.

- Polioviruses—all types.

- Rickettsia—members.

- Reviruses—all types.

- Respiratory syncytial virus.

- Rhinoviruses—all types.

- Rickettsia—all species.

- Rubella virus.

- Simian viruses—all types.

- Tick-borne encephalitis virus complex, in-
  cluding a subsection of a section of agents.

- Variola virus.

- Varicella virus.

- Varicella major and Variola minor viruses.

- Vesicular stomatitis virus.

- Yellow fever virus.

(1) Volume less than 50 ml. Material shall be placed in a securely closed, watertight container (primary container test tube, vial, etc.) which shall be encased in a second, durable water tight container (secondary container), and gential primary containers may be contained in a single secondary container, if the total volume of all the primary contain-

- Vehicle less than 50 ml. Material shall be placed in a securely closed, watertight container (primary container test tube, vial, etc.) which shall be encased in a second, durable water tight container (secondary container), and gential primary containers may be contained in a single secondary container, if the total volume of all the primary contain-

- Vehicle less than 50 ml. Material shall be placed in a securely closed, watertight container (primary container test tube, vial, etc.) which shall be encased in a second, durable water tight container (secondary container), and gential primary containers may be contained in a single secondary container, if the total volume of all the primary contain-

- Vehicle less than 50 ml. Material shall be placed in a securely closed, watertight container (primary container test tube, vial, etc.) which shall be encased in a second, durable water tight container (secondary container), and gential primary containers may be contained in a single secondary container, if the total volume of all the primary contain-

- Vehicle less than 50 ml. Material shall be placed in a securely closed, watertight container (primary container test tube, vial, etc.) which shall be encased in a second, durable water tight container (secondary container), and gential primary containers may be contained in a single secondary container, if the total volume of all the primary contain-
between the primary and secondary containers, at the top, bottom, and sides between the secondary container and the outer shipping container. Single primary containers shall not contain more than 500 ml of material. However, two or more primary containers whose combined volumes do not exceed 500 ml may be placed in a single, secondary container. Not more than eight secondary shipping containers may be enclosed in a single outer shipping container. (The maximum amount of etiologic agent which may be enclosed within a single outer shipping container shall not exceed 4,000 ml.)

(3) Dry ice. If dry ice is used as refrigerant, it must be placed outside the secondary container(s). If dry ice is used between the secondary container and the outer shipping container, the shock absorbent material shall be so placed that the secondary container does not become loose inside the outer shipping container as the dry ice sublimes.

(4) Labels. The label for Etiologic Agents/Biomedical Material, except for size and color, must be as shown:

![Label](image)

(i) The color of material on which the label is printed must be white and the symbol and printing in red.

(ii) The label must be a rectangle measuring 51 mm. (2 inches) high by 102.5 mm. (4 inches) long.

(iii) The red symbol measuring 38 mm. (1 1/2 inches) in diameter must be centered in a white square measuring 51 mm. (2 inches) on each side.

(iv) Type size of the letters of label shall be as follows:

**ETILOGIC AGENT**

**BIOMEDICAL MATERIAL**

**IN CASE OF DAMAGE OR LEAKAGE**

**NOTIFY DIRECTOR CDC**

**ATLANTA, GA.**

7-point

10-point

10-point

8-point

10-point

(5) Damaged packages. Carriers shall promptly, upon discovery of damage to the package that indicates damage to the primary container, isolate the package and notify the Director, Center for Disease Control, 1600 Clifton Road NE., Atlanta, GA 30333 (telephone (404) 633-5313), and the sender.

(6) Registered mail or equivalent system. Transportation of the following etiologic agents shall be by registered mail or an equivalent system which requires or provides for sending notification to the shipper immediately upon delivery:

- *Actinobacillus melleti*
- *Coxiella burnetii*
- *Francisella (Pasteurella) tularensis*
- *Francisella (Pasteurella) tularensis*
- *Haemophilus influenzae*
- *Haemophilus influenzae*
- *Herpesvirus simiae* (B virus)
- *Hepatitis virus*
- *Lassa virus*
- *Marburg virus*
- *Pseudomonas pseudomallei*
- *Tick-borne encephalitis virus complex*, including, but not limited to, Russian spring-summer encephalitis, Kyasanur forest disease, Omak hemorrhagic fever, and Central European encephalitis viruses, Variola minor and Variola major.
- *Yersinia (Pasteurella) pestis*

(d) Notice of delivery; failure to receive. When notice of delivery of agents containing, or suspected of containing, etiologic agents listed in paragraph (c) of this section is not received by the sender within 5 days following anticipated delivery of the package, the shipper shall notify the Director, Center for Disease Control, 1600 Clifton Road NE., Atlanta, GA 30333 (telephone (404) 633-5313).

(e) Requirements; variations. The Administrator may approve variations from the requirements of this section if, upon review and evaluation, he finds that such variations provide protection at least equivalent to that provided by compliance with the requirements specified in this section and makes such findings a matter of official record.

Sec. 511, 58 Stat. 703; 42 U.S.C. 264)

Effective July 30, 1972
The Interstate Quarantine Regulations (42 CFR, Part 72.26 EtioLogic Agents) were revised July 31, 1972 to provide for packaging and labeling requirements for etiologic agents and certain other materials shipped in interstate traffic.

Figures 1 and 2 diagram the packaging and labeling of etiologic agents in volumes of less than 50 ml, in accordance with the provisions of subparagraph (C) (1) of the cited regulation. Figure 3 illustrates the color and size of the label, described in subparagraph (C) (4) of the regulations, which shall be affixed to all shipments of etiologic agents.

For further information on any provision of the regulation contact:
Center for Disease Control
Attn: Biohazards Control Office
1600 Clifton Road
Atlanta, Georgia 30333
Telephone: 404 633 3311

FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
PACKAGING AND LABELING OF ETIOLOGIC AGENTS

ABSORBENT PACKING MATERIAL

PRIMARY CONTAINER (Bottle, blood bag, etc.)

*NOTE: Single primary containers may not exceed 500 ml. of material. Two or more primary containers whose combined volumes do not exceed 500 ml. may be enclosed in a single, secondary container. The maximum volume of etiologic agent which may be enclosed in a single outer shipping container shall not exceed 4000 ml.

SHOCK ABSORBENT MATERIAL

SECONDARY CONTAINER (Gasketed screwcap with waterproof tape or hermetically sealed can)

OUTER SHIPPING CONTAINER

MAILING LABEL

ETIOLOGIC AGENT LABEL

The Interstate Quarantine Regulations (42 CFR, Part 72.25, Etiologic Agents) was revised July 31, 1972, to provide for packaging and labeling requirements for etiologic agents and certain other materials shipped in interstate traffic. The illustration shows acceptable packaging and labeling of etiologic agents in accordance with subparagraphs (c) (2) and (4) of the cited regulation.

For further information on any provision of this regulation contact:
Center for Disease Control
Attn: Biohazards Control Office
1600 Clifton Road
Atlanta, Georgia 30333

Telephone: 404-633-3311
NOTICES

XII. OUTLINE OF A SAFETY AND OPERATION MANUAL FOR A P4 FACILITY

A. Purpose.
B. Policy.
C. Responsibility and Authority. 1. Management.
D. Supervisor.
E. Each Employee.
F. Facility Safety Officer.
G. Biohazard Containment Committee.
H. Facility Assignment Procedures.
I. Reporting of Major and Minor Accidents and Injuries, Exposure to Toxic or Infectious Materials, Unsafe Conditions and Property Damages, and Rendering First-Aid.
J. General Laboratory Safety. 1. Fire.
K. Equipment.
L. Physical.
M. Chemical.
N. Radiological.
O. Safety Procedures Associated with Biohazard Activities of the Laboratory. 1. Personnel Practices.

II. Operational Practices.
A. Medical Surveillance.
C. Access Procedures for Equipment Materials and Supplies.
D. Maintenance and Support.
E. Zone Classification.
F. Facility Monitoring Procedures.
G. Housekeeping.
H. Others. 1. Packaging and Shipment of Biohazardous Materials.
I. Emergency Procedures.
J. Insect and Rodent Control.
K. Orientation and Training.

Appendix 1. Biohazard and Injuries

Appendix 2. Biohazard and Injury Control

Appendix 3. Biohazard and Injury Control

Appendix 4. Biohazard and Injury Control

Appendix 5. Biohazard and Injury Control

REFERENCES


FEDERAL REGISTER, VOL. 41, NO. 176—THURSDAY, SEPTEMBER 9, 1976
33. Code of Federal Regulations, Title 9—Animals and Animal Products. For sale by Supt. of Documents, Government Printing Office, Washington, D.C. 20402. (In the capital city of most states, a copy limited to Chapter 1, Subchapter A, Parts 1, 2, 3 can be obtained from the Federal Veterinarian in Charge, Animal and Plant Health Inspection Service.)

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